TOTAL SYNTHESES OF ANTITUMORAL (±)-MAFAICHEENAMINE A, UNNATURAL 6-FLUOROMAFAICHEENAMINE A AND NATURALLY OCCURRING A TYROSINE DERIVATIVE

BY

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Dedicated to my beloved parents and brothers.

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In the name of Allah, the Most Beneficent, the Most Merciful.

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ABSTRACT

Full Name : Yasir Abbas

Thesis Title : Total syntheses of antitumoral (±)-mafaicheenamine A, unnatural 6-fluoromafaicheenamine A and naturally occurring a tyrosine derivative

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Cancer is the second leading cause of death. As such, discovery and development of anticancer agents has attracted a great deal of attention by several pharmaceutical companies as well as non-profit organizations. Almost half of the approved anticancer agents are either natural products or semi-synthetic derivatives derived their off. Recently, phytochemical investigation of twigs of *Clausena lansium* has led the isolation of a new carbazole alkaloid, mafaicheenamine A (**1**). While exhibiting moderate activity against KB ($1C_{50}$ = 7.68 μg/mL) and NCI-H187 ($1C_{50}$ = 13.27 μg/mL), compound **1** showed potent activity against MCF7 ($1C_{50}$ = 2.96 μg/mL). In this study, the synthesis of compound **1** was successfully accomplished. In view of the importance and utility of fluorine substituents in drug discovery, the usefulness of our synthetic approach was extended towards the synthesis of 6-fluoromafaicheenamine A (**2**), an unnatural analogue of **1**. On the other hand, bioassay-guided isolation from the broths of *Streptomyces sp*. IFM 10937 has led to a new tyrosine derivative **3** which possess very promising trail-resistance-overcoming activity. Consequently, the synthesis of compound **3** was also targeted and achieved successfully in the course of this study.

ملخص الرسالة

الاسم الكامل: ياسر عباس

عنوان الرسالة: مجموع خلاصات مضاد للأورام mafaicheenamine A-(±)، غير طبيعي 6- fluoromafaicheenamin A والتي تحدث بشكل طبيعي مشتق التيروزين

التخصص: كيمياء

تاريخ الدرجة العلمية: مايو, 2016

السرطان هو السبب الرئيسي الثاني للوفاة. على هذا النحو، واكتشاف وتنمية العوامل المضادة للسرطان وقد اجتذب قدرا كبيرا من الاهتمام من قبل العديد من الشركات الدوائية وكذلك المنظمات غير الهادفة للربح. ما يقرب من نصف العوامل المضادة للسرطان إما المنتجات الطبيعية أو المشتقات شبه التركيبية المستمدة من الطبيعة. في الآونة الأخيرة، حديثاً التحقيق الكيميائي النباتي من اغصان *Clausena lansium* أدى عزل الجديد carbazole alkaloid، (**1**)mafaicheenamine A. في حين أنه يظهر النشاط المعتدل ضد KB (IC_{50} = 7.68 ميكروغرام / مل) وNCI-H187 (C50 = 13.271 ميكروغرام / مل)، وأظهر مركب **1** النشاط قوية ضد MCF7 (IC_{50} = 2.96 ميكروغرام / مل). في هذه الدراسة، تم تحضير تركيب المركب 1 بنجاح. ونظرا لأهمية وفائدة مستبدلات الفلور في اكتشاف العقاقير، تم تمديد فائدة الطبيعة الاصطناعية لدينا نحو تخليق (**2**)6-fluoromafaicheenamine A، مشتقات غير طبيعي **1**. من ناحية أخرى، من قبل الأحيائي المساند من المرق *Streptomyces sp*. IFM 10937. أدى إلى التيروزين جديد مشتق **3** التي تمتلك نشاط واعد جدا للتغلب والمقاومة على TRAIL . ونتيجة لذلك، تحضير مركب **3** تم استهدافة وتحقق بنجاح في سياق هذه الدراسة أيضا.

CHAPTER 1

INTRODUCTION

1.1 Cancer:

Cancer, a genetically caused diseases, follows abnormality in cell growth and cell death pathways due to genomic alterations. The unrestrained cell growth that leads to accumulation of unwanted cells in the vicinity of normal cells eventually progresses to the form of tumor and then spreading to the different parts of a body (metastasis). Cancer still remains a huge torment worldwide since very limited advancement so far has been made to secure remedies for the treatment of this disease [1]. Recent reviews from the International Union Against Cancer and the American Cancer Society have disclosed that in the last year 12 million diagnosis of cancer occurrence have been reported whereas 7 million mortality have been caused worldwide and these mortalities are estimated to increase twofold by 2030 [2]. Apoptosis, a process of programmed sequence that results in cell death, is a biochemical process that eliminates undesirable cells and regulate tissue homeostasis genetically. Surgery, chemotherapy and radiotherapy are the major approaches for the treatment of cancer [3].

The use of incorrect diet, the environment and genetic predisposition can be the factors resulting in cancer but prediction for cancer cannot be made on these factors alone. All cancers begin with mutations in DNA and gene changes within cells. However, the initial causes of mutation still remains a mystery which in turn leads to impair the discovery in cancer treatment [4]. The mutation resulting in cancers could take years to progress to

its detrimental phase. The mutations in DNA or altered gene regulation can normally be corrected by normal cells but failure in such correction leads to unrestrained cell growth and consequently invasion of normal and local cells, leading to cancer [5].

1.2 Apoptosis:

Apoptosis is a process in which a cell follows a sequence on the way to death upon stimulation of a specific signal [6]. In the 1970's Kerr et al., were the first to investigate and study apoptosis and since then it has been remained a significant part of scientific attention. Factors that activate apoptosis include p53, a tumor suppressor gene, and caspases, a cysteine protease family. Any mutation or alteration in p53 disrupt the functioning of the apoptotic process which in turn escalates tumor progression. The activated caspases enzymes are responsible for the degradation of nuclear DNA and breakdown of critical proteins, cytoskeleton and nuclear membrane. Any obstruction in the functioning of caspases causes hindering of the apoptosis process. The death receptor cells also play an important role in the regulation of apoptosis. Any malfunctioning or incorrect signaling to these death receptor cells can also leads to inhibition of apoptosis and, hence, to the progression of cancer [7].

The genomic alterations in cancers cause the deregulation of cell growth and cell death pathways, which eventually leads to the relentless cancer cell growth at the expense of cancer cell death. Therefore, targeting cancer growth pathways to develop therapeutics that could trigger apoptotic pathways is gaining increasing focus from the research community. Since apoptosis initiation is governed by both the mitochondria-involved intrinsic pathway and death receptors-mediated extrinsic pathway, the eventual target of

such therapies is to restore endogenous death pathways in order to drive cancer cells into self-destruction. Among the several cell death pathways, apoptosis is the best characterized. Hence, apoptosis plays an important role both in carcinogenesis and cancer treatment. Consequently, several therapeutic agents targeting apoptosis are currently in clinical trials [8].

1.3 Tumor necrosis factor-related apoptosis inducing ligand (TRAIL)

Tumor necrosis factor-related apoptosis inducing ligand (TRAIL), a tumor necrosis factor (TNF) family member [9, 10], selectively activates apoptotic pathways in cancer cells [11] by binding on the death receptors DR4 [12, 13] and DR5 (Figure 1) [14, 15]. After initiation by the death-receptor pathway, TRAIL-induced apoptosis results in activation of effector caspase-3, death-inducing signaling complex (DISC) formation and proteolytic activation of caspase-8 [16].

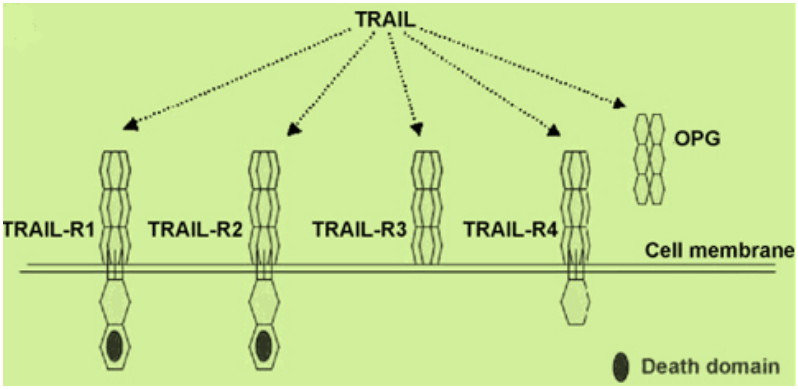


Figure 1 TRAIL receptor system

In addition, death receptors belong to the tumor necrosis factor receptor (TNFR) family that can engage intracellular apoptotic pathways.

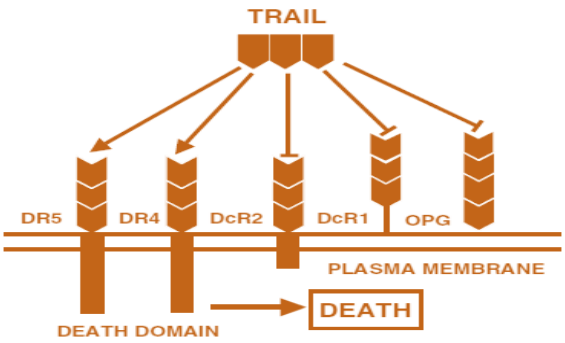
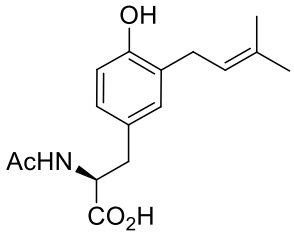


Figure 2 Trail and its receptors

The two approaches that have been employed to target TRAIL apoptotic pathway are recombinant human TRAIL (rhTRAIL) ligands and its agonistic antibodies against DR4 and DR5. These TRAIL agonists are currently in phase I-II clinical trials and are expected to lead to the genesis of a new class of anticancer therapeutics targeting apoptotic pathways. However, many hurdles yet to be overcome until these TRAIL agonists can be developed into effective clinical cancer therapeutics [16].

TRAIL has emerged as an attractive antineoplastic agent due to its remarkable ability of killing selectively tumoral cells while leaving normal cells unscathed [17]. Unlike the other members of the TNF superfamily, *in vivo* administration of TRAIL has been proven to be safe [18]. However, in the case of highly malignant tumors, a reasonable numbers of cancer cells have intrinsic or acquired resistance to TRAIL-induced apoptosis [19]. Therefore, discovery of compounds that can abrogate TRAIL resistance has attracted a great deal of attention in anticancer drug discovery.

In a recent study, bioassay-guided fractionation of *Streptomyces sp*. IFM 10937, has led to the isolation of a new tyrosine derivative **3** (Figure 3) [12]. Compound **3** was evaluated for its activity in overcoming TRAIL resistance in AGS (human gastric adenocarcinoma) cells. Combined treatment of 75 or 150 μM of **3** and 100 ng/mL TRAIL with AGS cell lines reduced cell viability to 77 ± 7% and 67 ± 5% of control levels ($p < 0.01$), respectively, which suggested a possible synergism between the two agents.



3

Figure 3 Chemical structure of tyrosine derivative 3

1.4 Natural products as anti-cancer agents

Nature is a fascinating foundation of novel medicinal compounds with a remarkable chemical diversity, originating from millions of species of plants, animals, marine organisms and microorganisms as potent anti-cancer agent [20]. The first known remedy for malignant tumors from plant–derived natural products was the roots of the autumn crocus (*Colchicum autumnale*), described by the Greek physician Dioscorides in ca. 50 A.D [21]. The alkaloid colchicine (**37**, Figure 4) was subsequently isolated from *C. autumnale* [22]. In the year 1958, elatericins A and B (**38** and **39**, Figure 5) were isolated

from *Ecballium elaterium* L. which showed strong activity against mouse sarcoma cells [23].

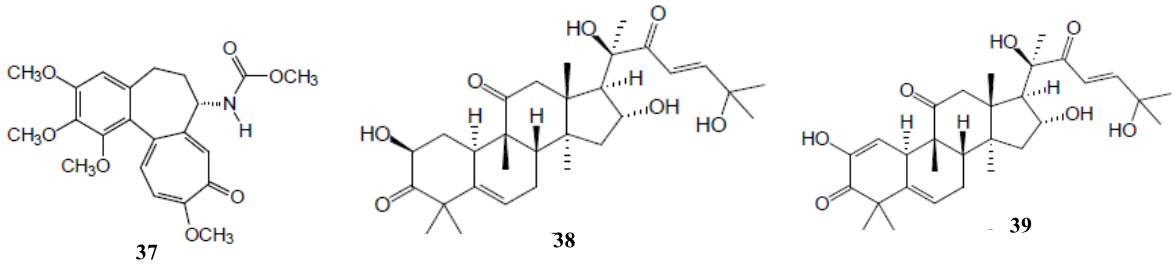
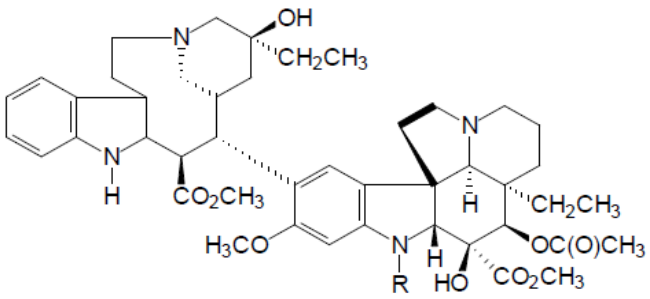


Figure 4 Colchicine, vinblastin and vincristine

Soon after, the famous alkaloids vinblastine and vincristine (**40** and **41**, Figure 5) were discovered from *Catharanthus roseus* [24]. These antitumor alkaloids have shown activity against a variety of cancer types including lymphoma, leukemia, breast, and lung [25], and their semi-synthetic analogues are used as remedies for the treatment of breast and lung cancers as well as various leukemias [26].

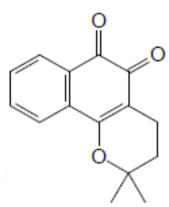


40 R = CH_3 Vinblastine
41 R = CHO Vincristine

Figure 5 Vinca alkaloids, vinblastin and vincristine.

In the year 1937, the establishment of the National Cancer Institute (NCI) spurred a major resurgence in anti-cancer drug discovery. More than 500,000 compounds for

potential cytotoxic activity [19] have been screened by the NCI since the last 50 years [27]. Several natural products such as β-lapachone (**42**) [28], combretastatin A_4PO_4 (**43**) [29], and betulinic acid (**44**) [30] have been isolated and advanced to either preclinical or clinical trials (Figure 6).



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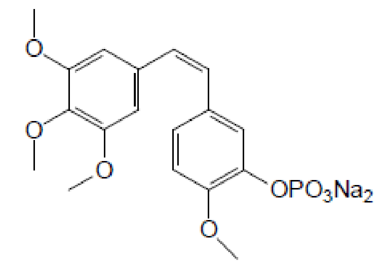

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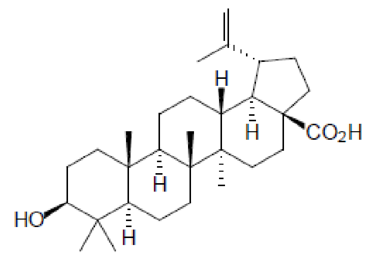

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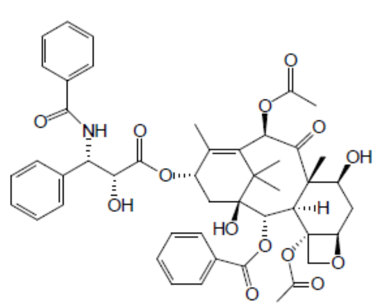
Figure 6 β-Lapachone, combretastatin A4PO4, and betulinic acid

Taxol® (**45**, Figure 8) was isolated from the bark of the Pacific Yew in 1966 [31], which represent one of the most successful stories of plant-derived anti-cancer agent. Taxol® is being used against breast and colon cancers, refractory ovarian cancer and Kaposi’s sarcoma [32]. As a result of taxol’s success, docetaxel (Taxotere®) (**46**, Figure 7) was prepared by Potier and coworkers and is used in the treatment ovarian, breast, and various lung cancers [33].



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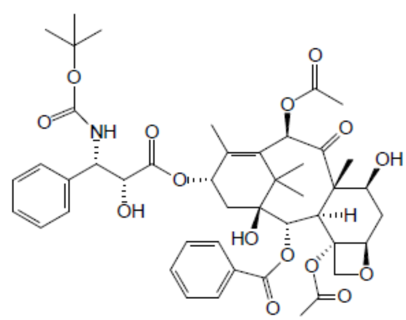
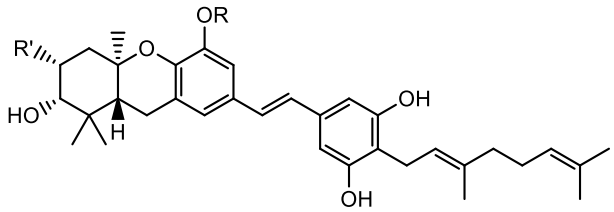


46

Figure 7 Taxol and docetaxel.

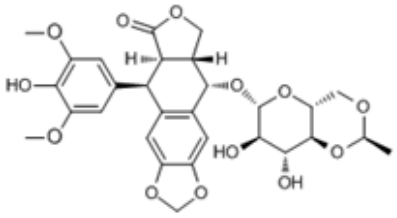
Schweinfurthins is a family of unique natural products that displayed potent anti-cancer activities in the NCI's 60–cell line; for instance schweinfurthins A and B (**47** and **48**, Figure 8) are potent and selective anti–proliferative agents.



47 R = H; R' = OH Schweinfurthin A
48 R = H; R' = CH_3 Schweinfurthin A

Figure 8 Schweinfurthins A and B.

Etoposide (**49**, Figure 9) is an epipodophyllotoxin, derived from the mandrake plant *Podophyllum peltatum* and the wild chervil *Podophyllum emodi*. It has shown efficacy in testicular cancer when used in combination with bleomycin (also derived from a natural product) and cisplatin and have shown activity against small-cell lung carcinoma. Likewise, homoharringtonine (**50**, Figure 9), an alkaloid isolated from *Cephalotaxus harringtonia* (Cephalotaxacea) [30] has shown efficacy against various leukemia [34].



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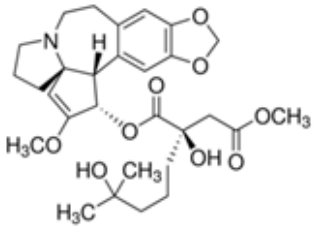

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Figure 9 Etoposide and homoharringtonine

Sorafenib (Nexavar, **51**, Figure 10) is a formal de novo new chemical entity which has been approved by the FDA in years 2005 and 2007 for the treatments of renal cell

carcinoma and hepatocellular carcinoma, respectively. The second drug that probably came about from a de novo sourcing is ataluren (Translarna, **52**, Figure 10), which was approved in the EU in the year 2014 for the treatment of patients with genetic disorders due to a "nonsense" mutation. However, the first anticancer drug constructed by use of fragment screening and model fitting, vemurafenib (Translarna, **53**, Figure 10), was approved by the FDA in 2011 [35].

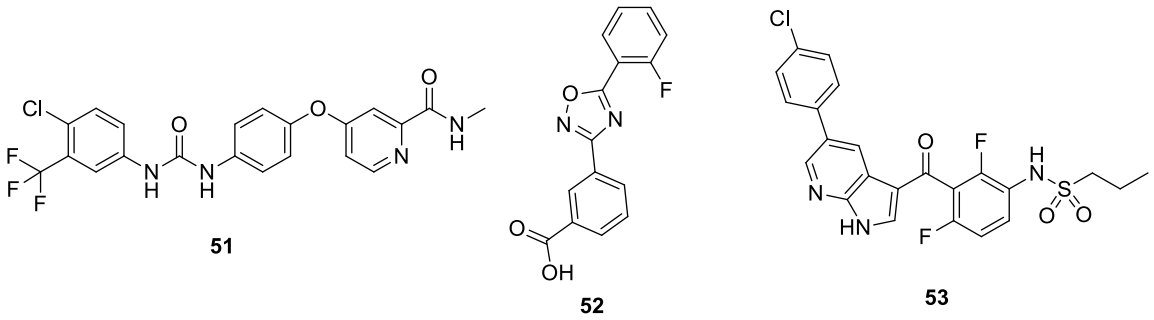


Figure 10 Sorafenib, ataluren and vemurafenib

CHAPTER 2

LITERATURE REVIEW

2.1 Literature review of Bioactive Carbazole Alkaloids

Carbazole alkaloids show a range of pharmacological activities including anti-cancer, anti-bacterial and anti-HIV activities [36, 37]. In addition, they possess effective cytotoxic activity against human leukemia cells, prostate cancer cell lines, viral and clinical pathogens [38-41].

Carbazomycin A and B, isolated from *Streptoverticillium ehimense,* inhibited the growth of phytopathogenic fungi and possess anti-yeast and antibacterial activities [42]. Carbazomycin G and H, isolated from the same plants, have become fierce synthetic targets because of their novel structures and their potent useful biological activities [43].

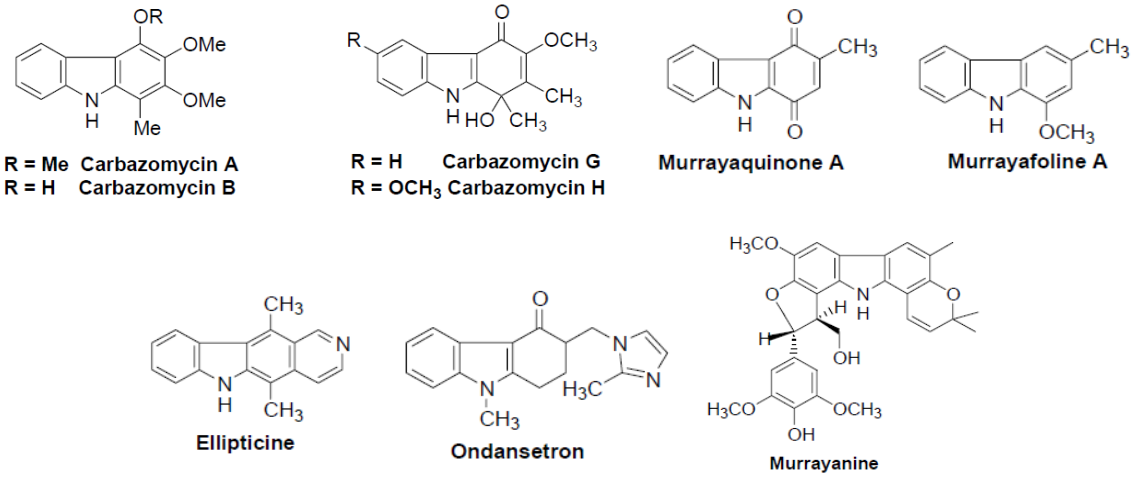


Figure 11 Structure of naturally occurring bio-active carbazole alkaloids.

Carbazole and their derivatives are strong antitumor agent. These derivatives exploit the activity DNA topoisomerase II resulting in inhibition of enzyme. These also interact with DNA in a manner resulting in covalent adducts that are facilitated by the oxidation with cytochromes P450 (CYP) and peroxidases [28].

Murrayafoline A and murrayquinone A, exhibiting cytotoxic activities, were isolated from *Murraya euchrestifolia* (Figure 11). Whereas murrayquinone A possess appreciable cytotoxic activity against SK-MEL-5 and Colo-205 cells [44], murrayafoline A was found to induce apoptosis and inhibit cell cycle [45]. Ellipticine and its derivatives have shown substantial antitumor and anti-HIV activities. The high activity against numerous types of cancers and reduced toxicity towards normal cells have increased immense interest in ellipticine [46]. Murrayanine (Figure 12), a novel carbazole alkaloid, was isolated from *Murraya koenigii* [47]. Murrayanine possessed cytotoxicity against cultured KB cells. Ondansetron (Figure 12), a carbazolone based synthetic drug has shown potent 5-HT3 receptor antagonist activity. Ondansetron is used to decrease acute sickness often linked to chemotherapy and radiotherapy in cancer treatment [48]. Dimeric carbazole alkaloids, clausenamine A and chrestifoline A (Figure 12) were isolated from *Clausena excavate* and *Murraya euchrestifolia* and *M. koenigii* (Rutaceae), respectively. These compounds have demonstrated minimum cytotoxicity towards some lung cancer and melanoma cells as well as weak subpanel selectivity [49-51].

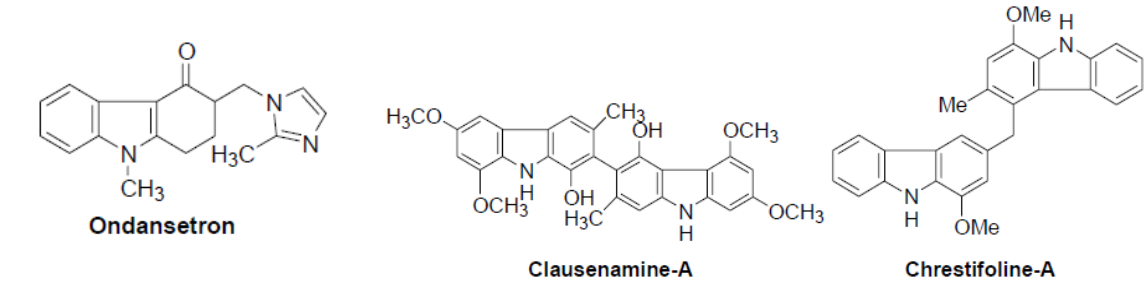


Figure 12 Structure of a synthetic and naturally occurring dimeric carbazole alkaloids

Itoa et al. isolated new carbazole from *Murraya koenigii*, exhibiting prominent cytotoxic activity against human leukemia cell line HL-60 cells. Mahanine, pyrayafoline-D, and murrafoline-I, (Figure 13) were capable in inducing apoptosis in HL-60 cells. The activity shown by these three alkaloids suggested they could be contenders for a cancer chemotherapeutic agent [52].

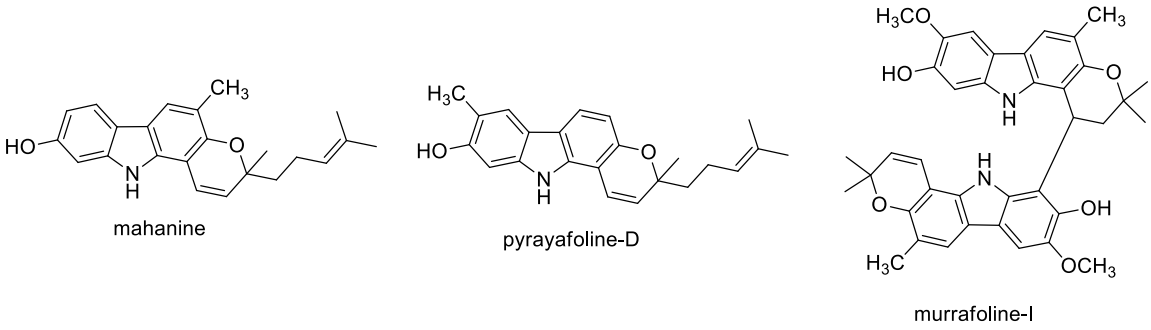


Figure 13 Chemical structure of carbazole alkaloids from Murraya koenigii.

Clausine–TH and Clausine–K (Figure 14) were isolated from the stem bark of *Clausena excavata*. These alkaloids have shown potent cytotoxicity against the CEM-SS cell lines with IC_{50} value of 2.1 µg/mL and 5.1 µg/mL, respectively [53].

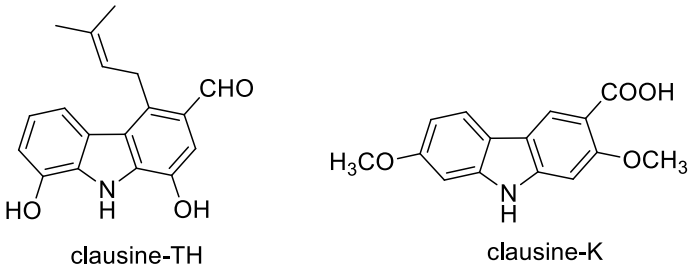
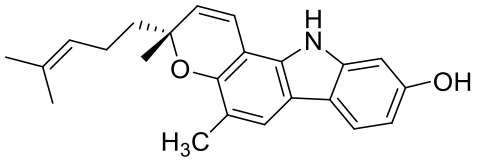


Figure 14 Chemical structure of Clausine-TH and Clausine-K.

Nakahara et al. has reported the isolation of an active alkaloid, (+)-mahanine (Figure 15) that exhibited a range of pharmacological activities such as antimutagenic towards heterocyclic amines such as Trp-P-1, cytotoxic activity against tumor cell line HL60 and antibacterial activity against *Bacillus cereus* and *Staphylococcus aureus* with MIC_{100} values of 6.25 and 12.5 μg/mL, respectively [54].



mahanine

Figure 15 Carbazole extracted from Micromelum minutum.

Ito et al. have isolated nine carbazole alkaloids (Figure 16) from *Clausena anisata* which have shown promising antitumor activities. The structure-activity relationship analysis on the existing antitumor carbazole alkaloids has suggested that ekeberginine might be valuable as antitumor promoters in chemical carcinogenesis [55].

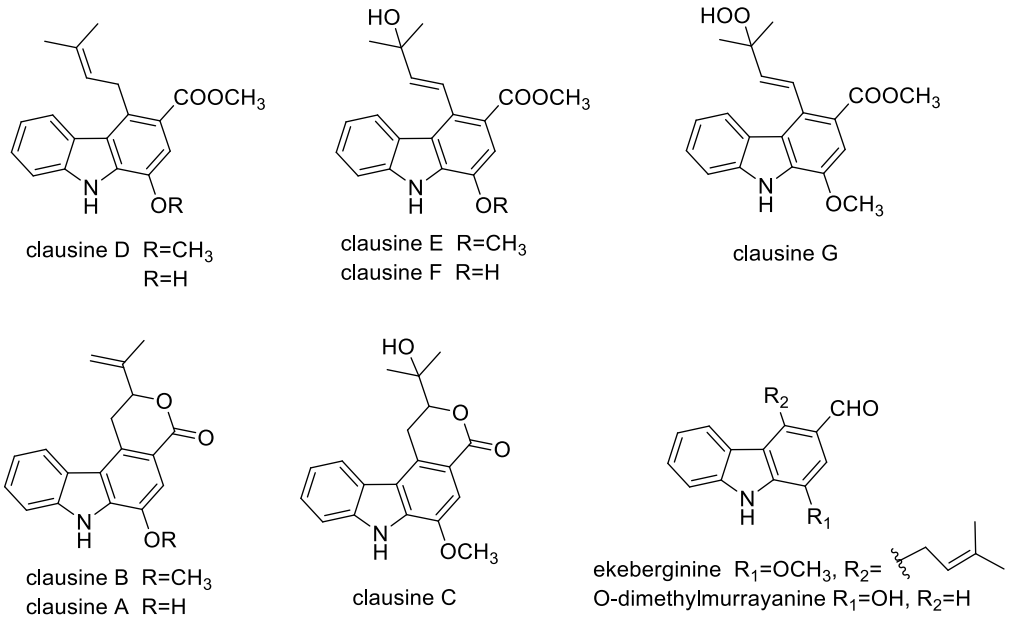


Figure 16 Nine isolated carbazole alkaloids from *Clausena anisata*.

Du et al. have reported ten new carbazole alkaloids, claulansines (**54-63**) and seven known analogues (**64-70** Figure 17) isolated from the stems of *Clausena lansium*. Pharmacological screening of these compounds have indicated that **54, 59, 61-63, 66, 67** and **70** showed selective neuroprotective effects [56].

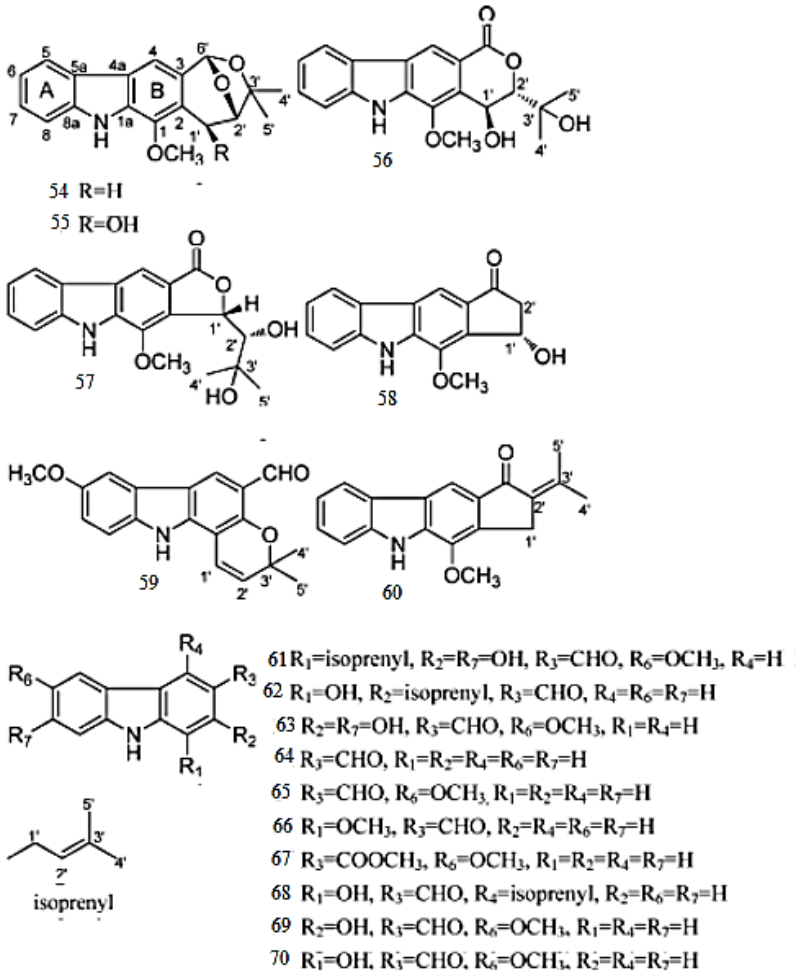
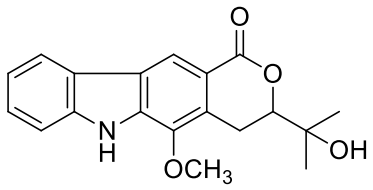


Figure 17 Carbazole alkaloids isolated from the stems of Clausena lansium.

Maneerat et al. have recently reported isolation and characterization of a new carbazole alkaloid named mafaicheenamine A **1** (Figure 19) from the twigs of *Clausena lansium* [51]. Compound **1** was screened for antitumor activity which revealed that **1** has potent activity ($1C_{50}$ = 2.96 µg/mL) against breast cancer (MCF7) and moderate activities against oral cavity cancer (KB, $1C_{50}$ = 7.68 µg/mL), and small lung cancer (NCI-H187, $1C_{50}$ = 13.27 µg/m1L).

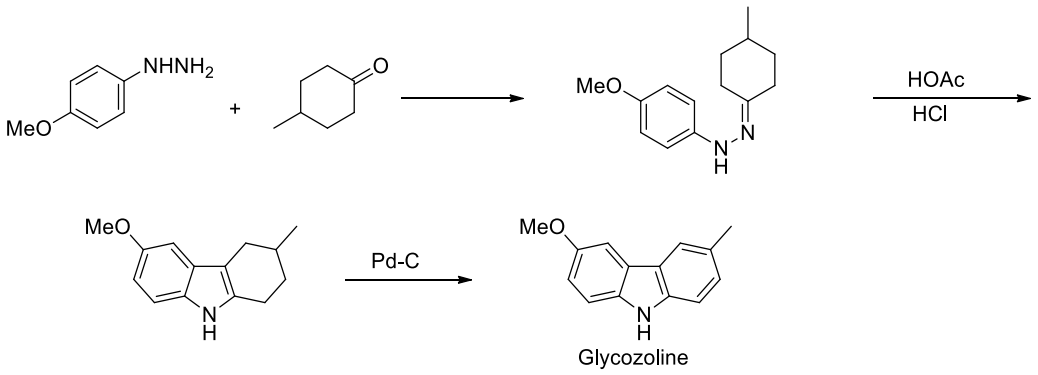


1

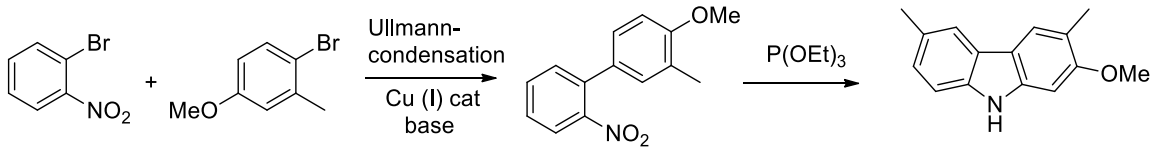
Figure 18 Mafaicheenamine A.

2.2 Literature review of Carbazole Alkaloid synthesis

The major syntheses endeavors of the alkaloids, particularly the older ones, are based on the well-known synthetic strategies those are based on the Fischer indole synthesis (Scheme l) or coupling of the two substituted benzene rings followed by cyclization (Scheme 2). The effectiveness of these synthetic methods is limited due to the lack of the regioselectivity and scarcity of different substituted cyclohexanones or benzenes coupling partners [57].

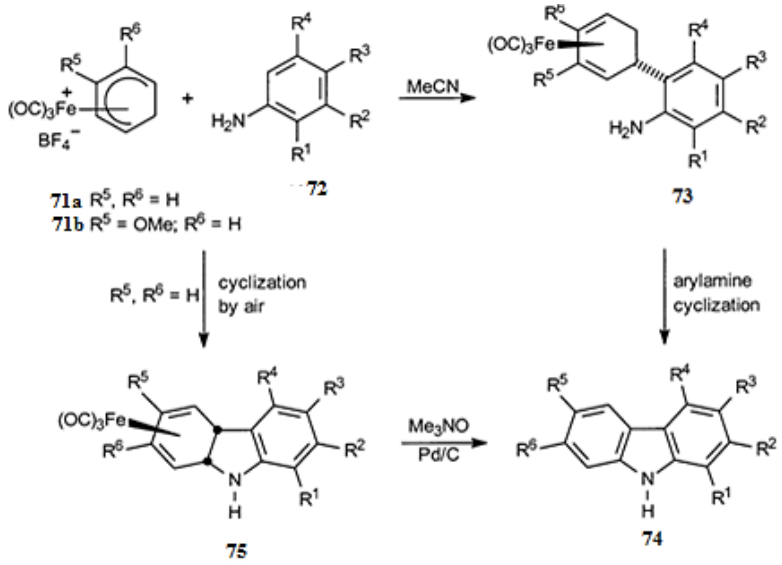


Scheme 1: Fischer Indole synthesis of carbazole



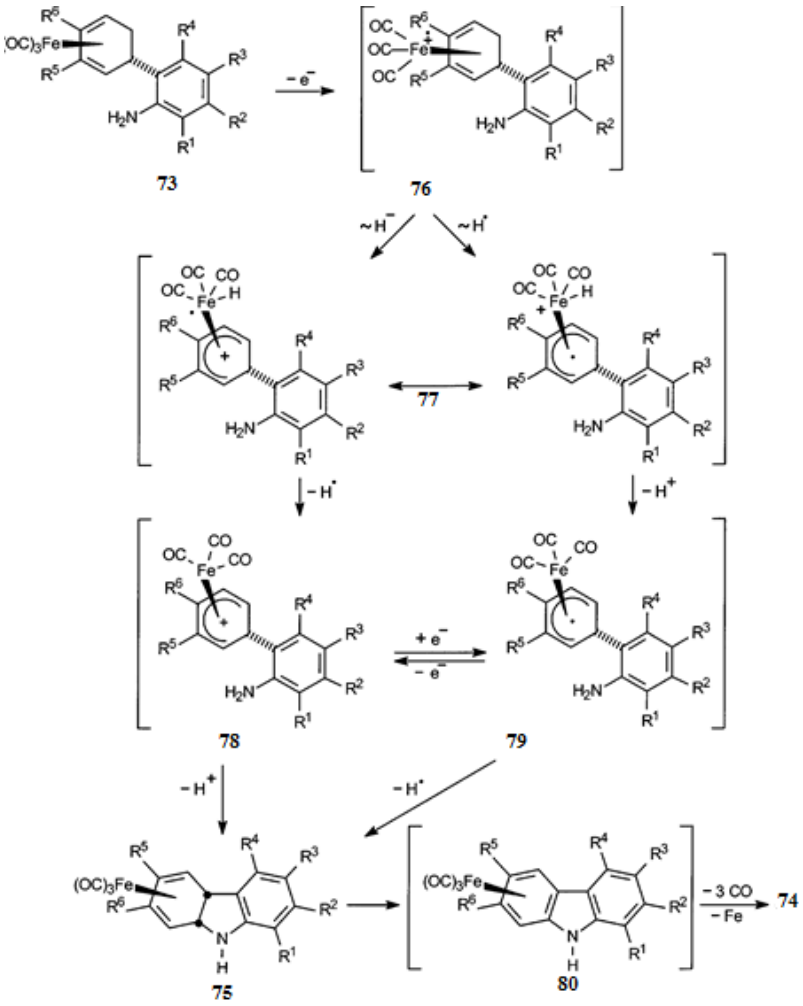
Scheme 2: Carbazole synthesis via Ullmann condensation

The electrophilic aromatic substitution of functionally diverse electron-rich arylamines **72** with tricarbonyliron-coordinated cyclohexadienylium ions **71** followed by concomitant oxidative cyclization of the arylamine-substituted tricarbonyl(η^4-cyclohexadiene)iron complexes **73** opened up the way to highly convergent total syntheses of a broad range of biologically active carbazole alkaloids **74**. Over the past decades different procedures for the ironmediated oxidative coupling of arylamines with a cyclohexadiene to carbazole derivatives (Scheme 3) have been developed [58].



Scheme 3: Iron mediated carbazole synthesis

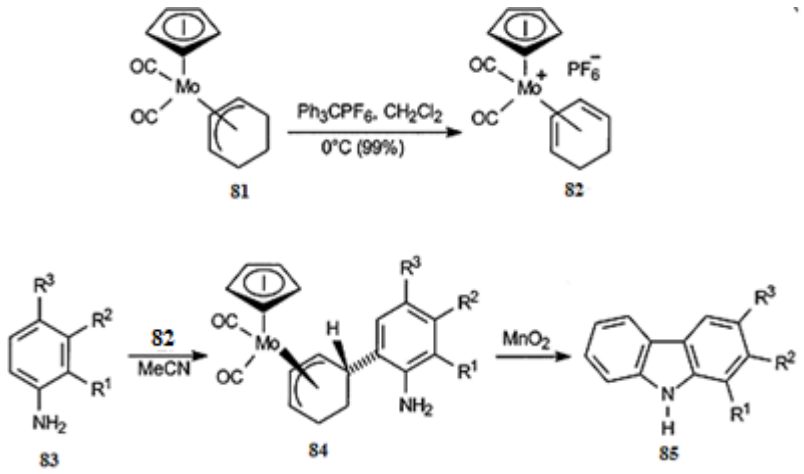
The one pot transformation of the arylamine-substituted tricarbonyl(η^4-cyclohexadiene)iron complex **73** to the 9*H*-carbazole derivative **74** proceeds via a sequence of cyclization, aromatization, and demetalation. The cyclizing dehydrogenation leads to the intermediate tricarbonyliron-complexed 4a,9a-dihydro-9*H*-carbazole **75** and subsequent intramolecular, syn-stereospecific hydrogen transfer afforded compound **77** [59].



Scheme 4: Mechanism for Iron catalyzed carbazole synthesis

The dehydrogenation via the tricarbonyl(η^5-cyclohexadienylium)iron derivatives **78** and **79** provides the dihydrocarbazole **75**. Further dehydrogenation affords the tricarbonyl(η^6-arene)iron complex **80**, which demetalates spontaneously to the carbazole derivative **74** (Scheme 4). This methodology has been widely used for the total synthesis of a broad range of 1-oxygenated, 3-oxygenated, and 3,4-dioxygenated carbazole alkaloids [60].

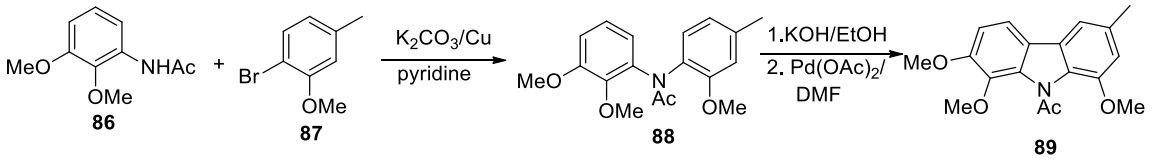
The electrophilic aromatic substitution of the electron-rich arylamines **83** by the molybdenum complexed cation **82** afforded regio- and stereoselectively the molybdenum complexes **84** which was subject to oxidative cyclization with concomitant aromatization and demetalation to produce the carbazole derivatives **85** (Scheme 5) [62].



Scheme 5: Molybdenum mediated carbazole synthesis

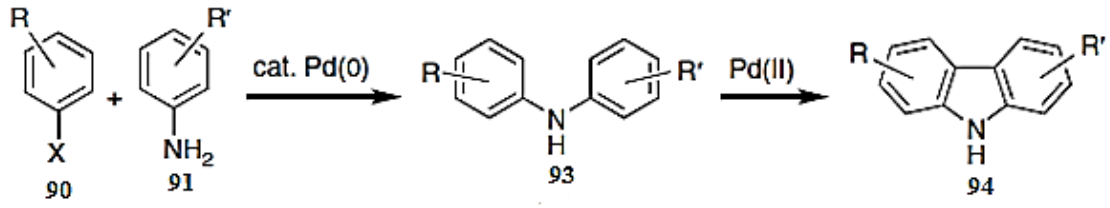
The cyclodehydrogenation of diphenylamines to carbazole derivatives has been accomplished with palladium(II) acetate catalyst. Furukawa et al. reported the synthesis of murrayastine **89**. Ullmann-Goldberg coupling of *N*-acetyl-2,3-dimethoxyaniline **86** and 2-bromo-5-methylanisole **87** with Cu and K_2CO_3 in pyridine followed by hydrolysis provided

the diarylamine **88**, which was subjected to cyclodehydrogenation with palladium(II) acetate to afford murrayastine **89** (Scheme 6) [63].



Scheme 6: Carazole synthesis via Ullmann-Goldberg coupling

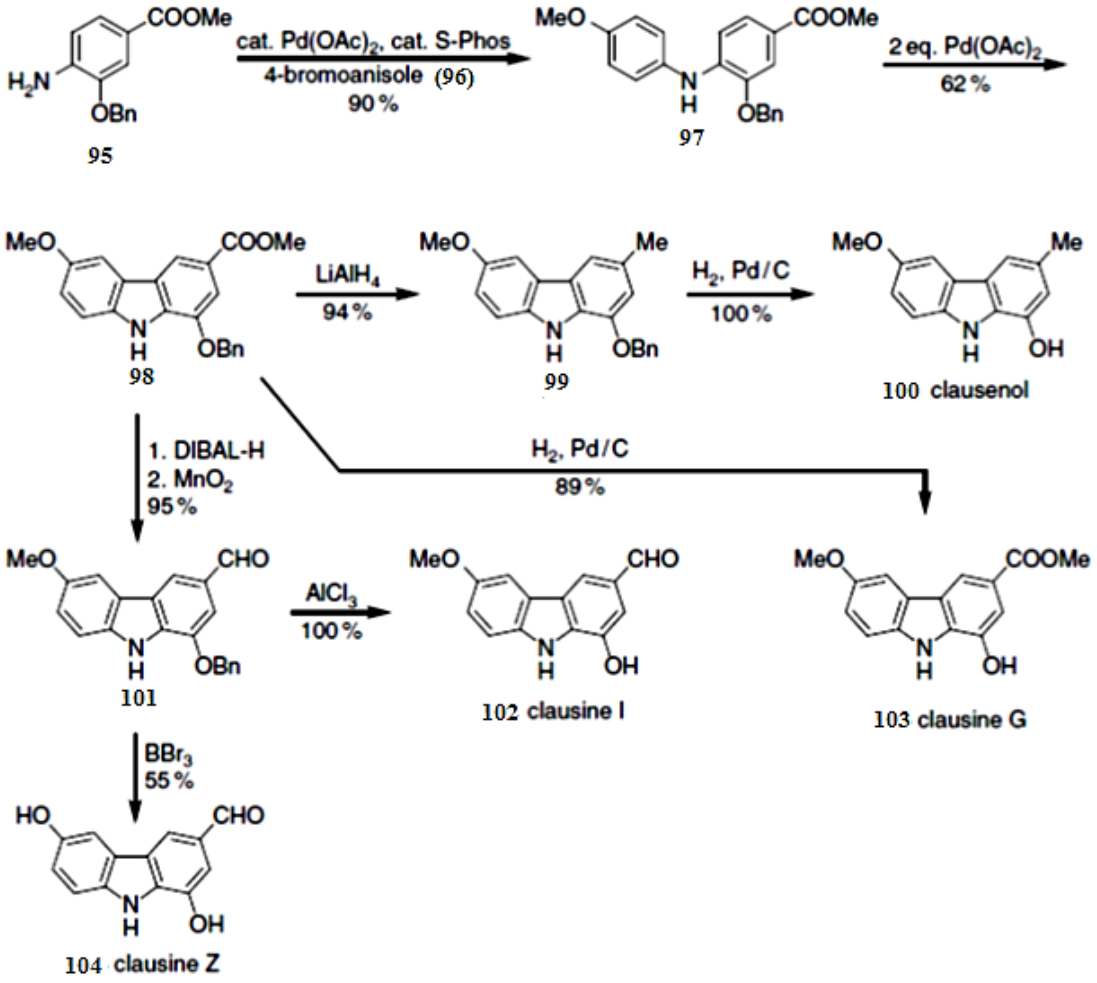
One of the most versatile approaches to highly functionalized carbazoles is the sequential palladium-catalyzed C–N/C–C coupling for assembly of the central pyrrole moiety. Many total syntheses of naturally occurring carbazole alkaloids are following this route. The initial C–N bond formation by Buchwald–Hartwig amination between aryl halides or triflates **90** with arylamines **92** afforded the diarylamines **93** (Scheme 7) which was then oxidative cyclized to the carbazoles **94** via a double C–H bond activation, using palladium(II) catalyst [64].



Scheme 7: Synthesis of carbazole 94 by Bucwald-Hartwig amination and subsequent oxidative cyclization of diarylamine 93

The first total synthesis of the 1,6-dioxygenated carbazole alkaloids clausine G **103**, clausine I **102**, and clausine Z **104** was achieved using palladium catalyzed approach (Scheme 8) [65]. Buchwald–Hartwig coupling of the arylamine **95** with p-bromoanisole **96** afforded the diarylamine **97** which in turn was subjected to oxidative cyclization to produce carbazole **98**. Clausine G **103** is readily prepared by catalytic debenzylation of the central

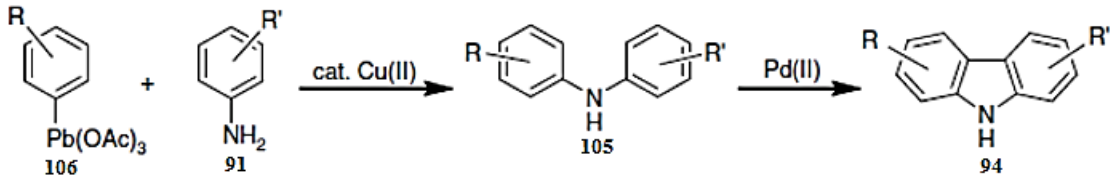
intermediate **98**. Reduction of ester function of **98** with lithium aluminum hydride gave compound **99**. The removal of the benzyl protecting group then eventually led to the synthesis of clausenol **100**. Likewise, reduction of intermediate **98** with DIBAL-H) and subsequent oxidation of the benzylic alcohol afforded the 3-formylcarbazole **101**.



Scheme 8: Palladium mediated catalytic synthesis of carbazole

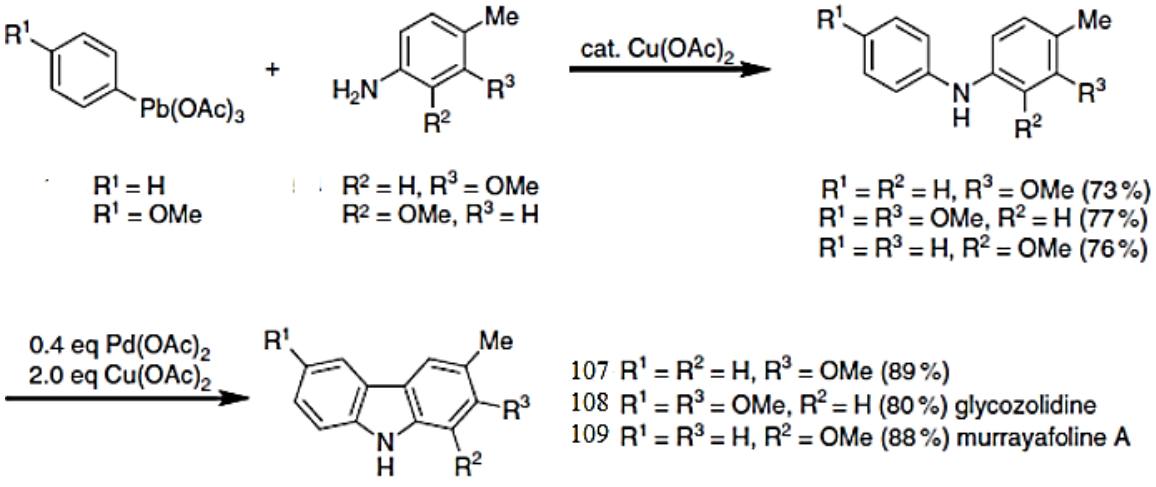
Construction of the carbazole framework involving the copper(II)-catalyzed arylamine arylation followed by palladium(II)-mediated oxidative cyclization has been reported by Menendez et al. (Scheme 9) [66]. The diarylamines **105**, obtained by copper(II) acetate-catalyzed N-arylation of arylamines **91** with phenyllead triacetate **106** was

subjected to oxidative cyclization using palladium(II) acetate under microwave irradiation to afford the carbazoles **94**.



Scheme 9: Copper catalyzed carbazole synthesis

This procedure was applied to the synthesis of murrayafoline A **109** [67]. The palladium(II)-catalyzed version with copper(II) acetate as co-oxidant, originally reported by Knolker et al. for the synthesis of murrayafoline A **109**, was employed for the synthesis of 2-methoxy-3-methylcarbazole **107**, and glycozolidine **108** (Scheme 10), as well as some non-natural carbazoles [68].



Scheme 10: Synthesis of natural carbazole using phenylleadtriacetate

CHAPTER 3

RESULTS AND DISSCUSSIONS

3.1 Synthesis of mafaicheenamine A

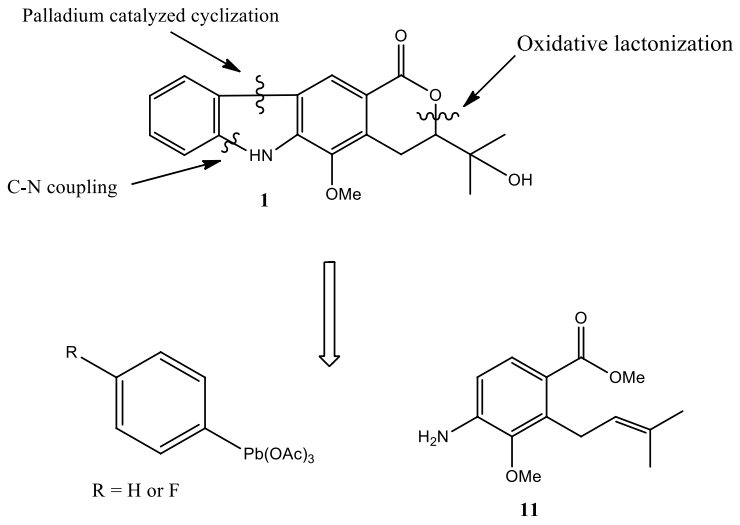
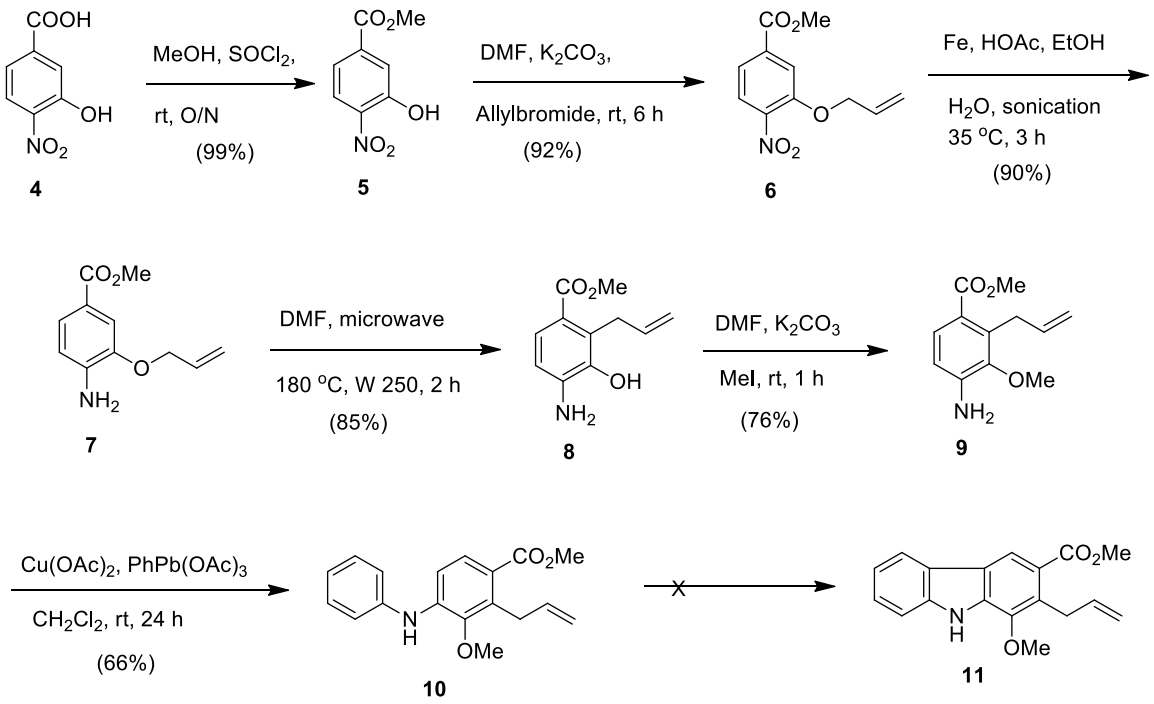


Figure 19 Retosynthetic analysis for mafaicheenamine A.

The synthesis of compound **1** was envisioned from intermediate **11** which was to be transformed to **1** by the operations of olefin metathesis followed by oxidative cyclization (Figure 20). To this end, ester **5** was reacted with allyl bromide in DMF, using K_2CO_3 as a base, to produce the known ester **6** [69]. The Claisen rearrangement of **6** to the corresponding C-allyl phenol in ortho-dichlorobenzene, N,N-dimethylaniline or DMF either by conventional heating or under microwaves was very low yielding (32%), requiring prolonged heating and higher reaction temperature (> 150 ^oC). In all the attempts, the reaction had led to the recovery of either hydrolyzed acid (in case of N,N-dimethylaniline) or starting material (in case of ortho-dichlorobenzene and DMF). Consequently, the nitro group of **6** was reduced with iron powder in a mixture of ethanol,

acetic acid and water promoted by ultrasonic irradiation, to generate 7 in high yield (90%) [70]. The initial attempts of Claisen rearrangement of **7** in N,N-dimethylaniline under conventional heating or microwave irradiation were very sluggish, resulting the formation of only 10% of the desired product. However, with an optimized condition the reaction in DMF under microwave irradiation at 180 ^{o}C for 2 h gave the desired rearranged phenol **8** in high yield (85%). The chemoselective methylation on the phenolic OH of **8** with diazomethane in diethyl ether did not go to the completion even with the use excess of diazomethane; the desired **9** was formed in a low yield (15%) along with the recovery of **8**. In a second attempt, methylation was realized by stirring the solution of **8** in DMF with 1.3 equivalent of K_2CO_3 for 30 min before adding 1.2 equivalent of iodomethane (Scheme 11). The amount of K_2CO_3 and short reaction time (1.5 h) was critical to obtain the desired **9** in high yield (76%). The N-arylation of ester **9** with bromobenzene under Buchwald-Hartwig conditions ($Pd(dba)_2$, BINAP) rendered the desired **10** in a very low yield (16%). The reaction become relatively cleaner when the combination of $Pd(OAc)_2$ and JohnPhos were used as catalyst and ligand, respectively. However, column chromatography purifications in this case turned out to be tedious and the desired **8** was obtained in low (20%) yield. Consequently, N-arylation of ester **9** was realized under Barton conditions [71], using phenylead triacetate and copper(II) acetate as a catalyst to furnish the desired **10** in good yield (66%). Cyclodehydrogenation of **10** in acetic acid or DMF with catalytic or stoichiometric amounts of palladium(II) acetate and copper(II) acetate using either thermal induction [72] or microwave heating [73] at elevated temperatures did not yield the desired **11**, the decomposition of **10** was observed in all cases (Scheme 12).



Scheme 11: Synthesis of intermediate 9

Failure in cyclodehydrogenation of **10** led us revised our synthetic strategy as outlined in scheme 12. N-arylation of ester **13** with phenylead triacetate under Barton conditions furnished the desired **14** in good yield (67%). The key step of cyclodehydrogenation on **14** was performed in acetic acid at 100 °C, using palladium(II) acetate as a catalyst to furnish the desired **16** in good yield (60%). Removal of O-benzyl protection of **16** with catalytic hydrogenation produced **18** (clausine E) in 34% overall yield from **13**. Despite the fact that six procedures for the synthesis of clausine E are known [74], our synthetic method provide an efficient access to the synthesis of clausine E in an overall high yielding reaction sequence. Next, **18** was reacted with allyl bromide in DMF, using K_2CO_3 as a base, to produce **20** which in turn was subjected to Claisen rearrangement under the optimized condition in DMF, using microwave irradiation at 180 °C for 2 h to afford the desired C-prenylated phenol **22** in 82% yield. The chemoselective methylation on the phenolic OH of **22** was realized with iodomethane in DMF to achieve **24** (Scheme 2).

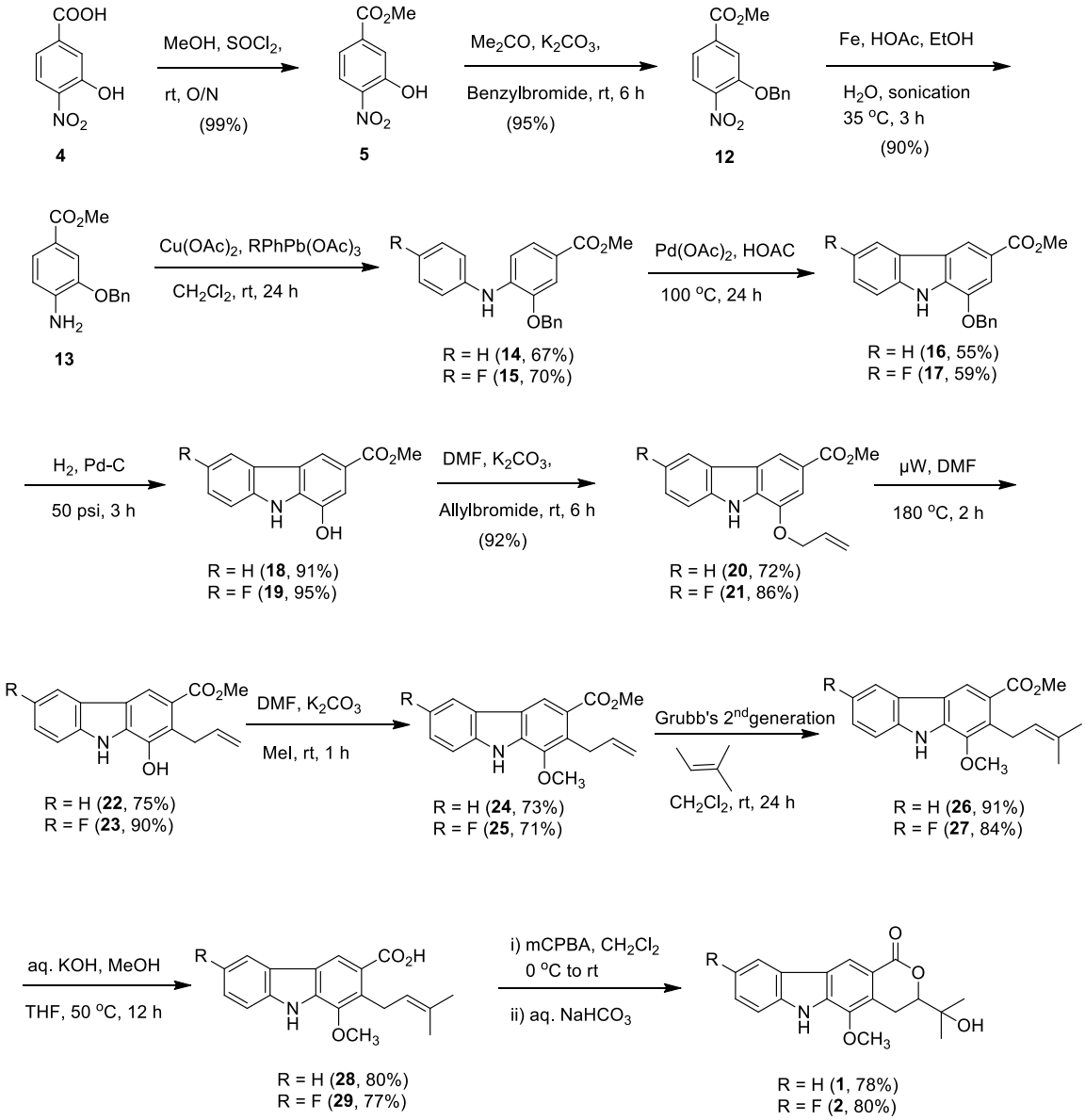
Olefin cross-metathesis reaction between intermediate **24** and 2-methyl-2-butene, using second-generation Grubbs catalyst yielded the desired **26** in excellent yield (91%). With compound **26** in hand, we next moved towards the construction of the dihydroisocoumarin unit of **1**.

To this end, acid **28** was treated with *m*-CPBA in CH_2Cl_2 followed by work-up with saturated $NaHCO_3$ readily generated the desired **1** in 78% yield (Scheme 2). All the spectral data of **1** matched with those of natural mafaicheenamine A [51].

Substitution of aromatic and heteroaromatic rings with fluorine substituent is a common practice in drug discovery. The incorporation of fluorine into a molecule can improve drug potency [75], target selectivity [76] and also can address issues associated with drug metabolism [77]. In a previous study, the effect of aromatic fluorine substitution in a series of thrombin inhibitors was investigated. The study revealed that incorporation of fluorine at C-4 of phenyl ring significantly enhanced the activity compared to when it was introduced at other positions of the phenyl ring. The high potency of 4-fluorophenyl derivative was rationalized due to the dipolar C–F…H–C_α and C–F…C=O interactions between the 4-fluorophenyl ring and the enzyme's active site [78].

Consequently, the usefulness of our synthetic approach was extended towards the synthesis of 6-fluoromafaicheenamine A (2), an unnatural analogue of 1. As depicted in Scheme 12, 6-fluoroclausine E **19** was synthesized from **13** by the reaction sequence of N-arylation with 4-fluorophenylead triacetate, palladium(II) acetate mediated cyclodehydrogenation and removal of benzyl protection with catalytic hydrogenation. Likewise intermediate **27** was originated from **19** by the operations of Pd-catalyzed

allylation, Claisen rearrangement and O-methylation. Finally basic hydrolysis of ester function of **27** followed by oxidative cyclization furnished the desired **2** (Scheme 13).



Scheme 12: Synthesis of mafaicheenamine A (1) and 6-fluoromafaicheenamine A (2)

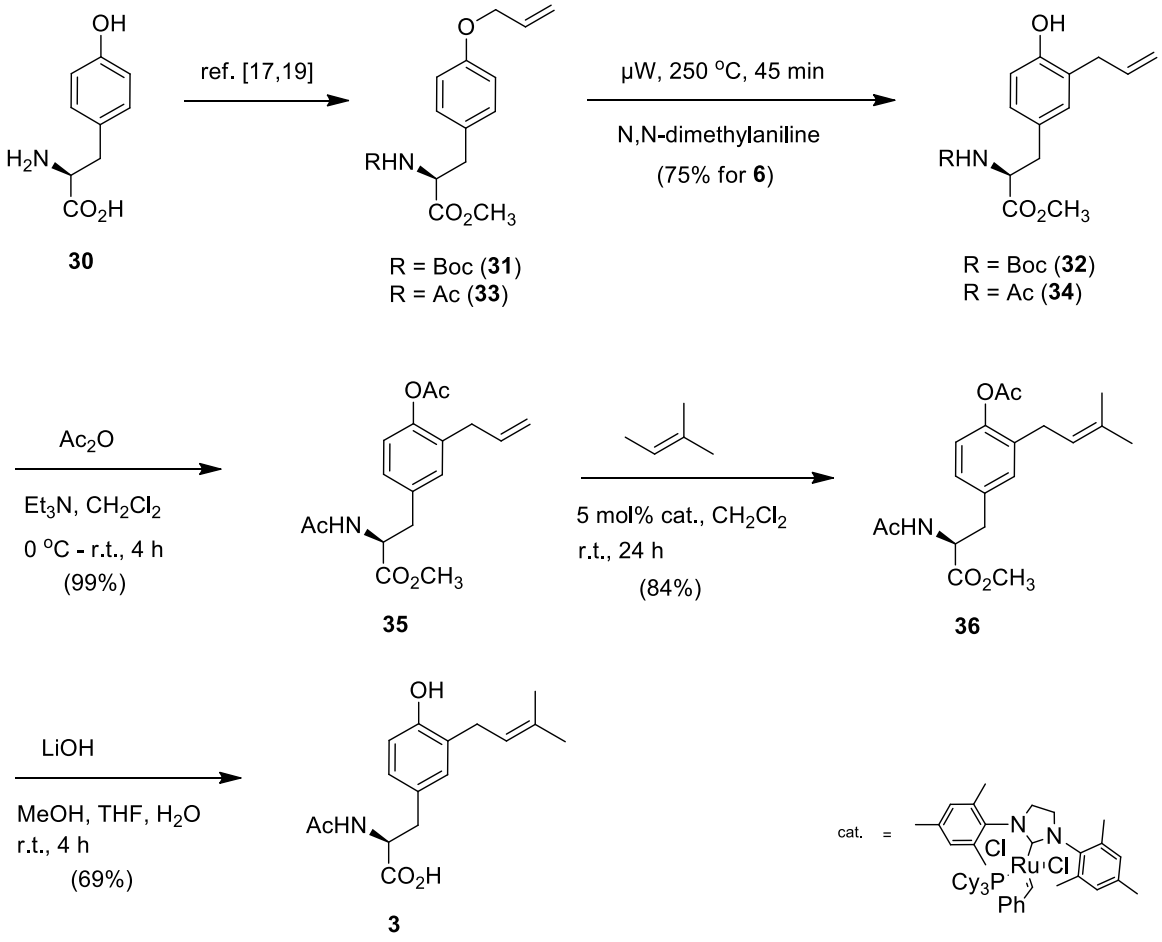
3.2 Synthesis of Tyrosine Derivative

Synthesis of the desired compound **3** was envisaged from the olefin cross-metathesis reaction of intermediate **32**, which in turn, was to be synthesized from Claisen

rearrangement of intermediate **31**. Thus, L-tyrosine **30** was converted to intermediate **31** by the operations of esterification, N-boc protection and O-allylation based on literature known procedures [79] (Scheme 13).

However, Claisen rearrangement of intermediate **31** either under thermal or microwave irradiation conditions at different temperatures, using N,N-dimethylaniline or DMF as solvents were unsuccessful. For instance, under thermal conditions reaction in N,N-dimethylaniline or DMF at reflux resulted the starting material intact whereas heating neat **31** at elevated temperatures led to the decomposition of **31**, with no desired product formation.

Likewise, under microwave conditions, reaction at lower temperature (200 ^{o}C, 250 W, 1 h) in DMF resulted unchanged **31** whereas heating the reaction at higher temperature (250 ^{o}C, 250 W, 45 minutes) in N,N-dimethylaniline had led to the deprotection of N-Boc group. Deprotection of N-Boc group under microwave conditions using mild base or under thermolytic conditions are well known [80]. To address the N-deprotection problem we moved on to make the N-acetyl derivative **33** which in turn was synthesized from intermediate **30** according to a literature known procedure [81] (Scheme 13). Claisen rearrangement of intermediate **33** in N,N-dimethylaniline under microwave irradiation at 250 ^{o}C gave the desired rearranged phenol **34** in excellent yield (75%). Acetylation of intermediate **34** under standard conditions rendered **35** in a very high yield. Olefin cross-metathesis reaction between intermediate **35** and 2-methyl-2-butene, using second-generation Grubbs catalyst yielded the desired **36** in excellent yield (84%).



Scheme 13: Synthesis of Tyrosine derivative (3)

It is noteworthy that O-prenylation of O-deallylated **33** followed by Claisen rearrangement would possibly have given access to the O-deacetylated **36**. Finally, exposure of intermediate **36** under basic condition at room temperature ultimately produced the desired **3** in 43% overall yield from **33** (Scheme 13). All the spectral data of **3** matched with those of the previously isolated material [12].

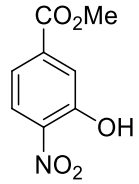
CHAPTER 4

EXPERIMENTAL

4.1 Material and Method

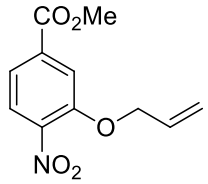
Pyrex glassware was used for the experimental needs. All glassware was washed and dried before use. For air and moisture sensitive reaction the glassware was washed and dried in an oven before initial use. Thin layer chromatography was systematically employed for the qualitative monitoring of the reactions performed and was frequently utilized while performing flash chromatography for the purification of the compounds synthesized. TLC analyses were executed on silica gel 60 F_{254} plates (E. Merck) and viewed under a UV lamp. Silica gel 100 from Fluka 44 Chemie AG (Buchs, Switzerland) was used for the packing of column. Chemicals were purchased from commercial sources, and they were used without any further purification unless otherwise specified. An inert atmosphere was used for reactions where necessary. Melting Points were determined on a Büchi apparatus (Büchi Labortechnik AG, Switzerland) and are uncorrected. Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400 (PerkinElmer Inc. USA). IR spectra were recorded on a NicoletTM 6700 FTIR spectrophotometer and were reported in wave numbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$, CD_3OD and d_6-DMSO using TMS as internal standard on a JEOL JNM-LA 500 MHz spectrometer (JEOL USA Inc.). Multiplicities were reported as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m), and coupling constants (J) were reported in hertz (Hz).

4.2 *Synthesis of methyl 3-hydroxy-4-nitrobenzoate (5)*



3-hydroxy-4-nitrobenzoic acid **4** (5g) was suspended in MeOH (50 mL) and stirred at 0ºC for 15 minutes followed by the addition of $SOCl_2$ (10 mL) drop-wise. The reaction was stirred overnight at room temperature and then evaporated under reduced pressure to get the title compound **5** as a yellow solid in quantitative yield. m.p. 83-85 ºC; IR (neat) 3306, 2959, 2920, 2850, 1722, 1621, 1586, 1521, 1474, 1434, 1323, 1282, 1223, 1145, 1098, 1065 cm^{-1}; ^{1} H-NMR (500 MHz; $CDCl_3$): δ 3.97 (s, 3H), 7.61 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.84 (d, *J* = 1.4 Hz, 1H), 8.17 (d, *J* = 8.8 Hz, 1H), 10.5 (s, 1H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 52.90, 120.58, 121.66, 125.25, 135.79, 137.98, 154.66, 164.81.

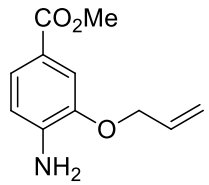
4.3 *Synthesis of methyl 4-nitro-3-(prop-2-en-1-yloxy)benzoate (6)*



To a solution of **5** (5 g, 25.36 mmol) in DMF (50) was added anhydrous K_2CO_3 (4.21 g, 30.43 mmol) followed by the addition of allyl bromide (2.57 mL, 30.43 mmol) e and the mixture was stirred overnight at room temperature. After consumption of starting material (TLC analysis), the reaction was quenched with water (50 mL) followed by the extraction with ethyl acetate (4 x 100 mL). The collective organic layers dried using Na_2SO_4 and

solvent removed using rotary evaporator to yield the title compound **6** as a pale yellow solid. Yield: 5.6 g, 93%: IR (neat) 3121, 2999, 2954, 1609, 1582, 1555, 1516, 1433, 1340, 1009, 981 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl3): δ 3.96 (s, 3H), δ 4.74-4.75 (d, *J* = 5.5 Hz, 2H), δ 5.34-5.37 (d, *J* = 10.6 Hz, 1H), δ 5.48-5.52 (dd, *J* = 18.6 Hz, 1H), δ 6.01-6.07 (m, 1H), δ 7.68-7.70 (dd, *J* = 1.8, 8.5 Hz, 1H), δ 7.74 (s, 1H), 7.82-7.33 (d, *J* = 8.2 Hz, 1H); ^{13}C-NMR (100 MHz, CDCl3): δ 52.84, 70.24, 115.92, 118.81, 121.57, 125.35, 131.35, 134.75, 142.73, 151.40, 165.20.

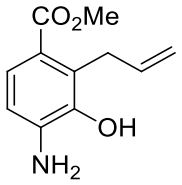
4.4 *Synthesis of Methyl 3-(allyloxy)-4-aminobenzoate (7)*



To a suspension of **6** (0.3 g, 1.3 mmol) in a mixture of glacial acetic acid (4 mL), ethanol (4 mL) and water (2 mL) was added reduced iron powder (0.37 g, 6.6 mmol). The resulting suspension was exposed to ultrasonic irradiation at 30 °C for 3 h and the mixture was filtered to remove the iron residue, which was washed with ethyl acetate (30 mL). The filtrate was added 2M KOH (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL) and water (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was resolved on silica column, eluting with hexanes-ethyl acetate (80:20) to afford the title compound **7** as a bright yellow oil. Yield: 0.25 g, 90%; IR (neat): 3373, 3312, 3025, 2946, 1682, 1608, 1573, 1571, 1426, 1363, 1302, 1208, 1136, 1101 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.85 (s 3H, OCH_3), 4.28 (br. s, 2H, NH_2), 4.60 (d, *J* = 5.5 Hz, 2H,

O*CH*$_2$CH=CH$_2$), 5.30 (dd, *J* = 1.5, 10.3 Hz, 1H, OCH$_2$CH=*CH*$_2$), 5.41 (dd, *J* = 1.5, 17.1 Hz, 1H, OCH$_2$CH=*CH*$_2$), 6.07 (m, 1H, OCH$_2$*CH*=CH$_2$), 6.67 (d, *J* = 8.2 Hz, 1H, H-5), 7.45 (d, *J* = 1.8 Hz, 1H, H-2), 7.54 (dd, *J* = 1.7, 8.2 Hz, 1H, H-6); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 51.66 (OCH_3), 69.23 (O*CH*$_2$CH=CH$_2$), 112.59, 113.27, 117.86, 119.39, 124.21, 132.98, 141.32, 144.95, 167.22 (C=O). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76%. Found: C, 63.72; H, 6.35; N, 6.71.

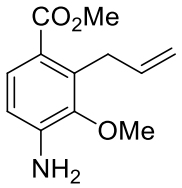
4.5 *Synthesis of Methyl 2-allyl-4-amino-3-hydroxybenzoate (8)*



In a microwave reaction vessel, through a solution of **7** (2.0 g, 9.7 mmol) in DMF (4 ml) was bubbled nitrogen for 1 min and vessel was then placed inside CEM Discover S-Class microwave synthesizer where it was exposed to microwaves at 180 ºC (260 W) for 2 h. After completion of the reaction, the mixture was diluted with ethyl acetate (50 mL), washed with water (10 mL) and then washed with brine (5 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Column chromatography purifications of the yellow oily material, eluting with hexanes-ethyl acetate (50:50) afforded compound **8** as an off white solid. Yield: 1.7 g, 85%; m.p. 91-92 ºC; IR (neat): 3408, 3313, 3002, 2947, 1693, 1601, 1493, 1441, 1277, 1191, 1100, 1015 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 3.89 (d, *J* = 6.1 Hz, 2H, Ar*CH*$_2$CH=CH$_2$), 4.12 (br. s, 2H, NH_2), 5.15-5.19 (m, 2H, OCH$_2$CH=*CH*$_2$), 6.06 (m, 1H, OCH$_2$*CH*=CH$_2$), 6.60 (d, *J* = 8.2 Hz, 1H, H-5), 7.50 (d, *J* = 8.2 Hz, 1H, H-6); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 31.64

(Ar*CH*$_2$CH=CH$_2$), 51.57 (OCH_3), 112.44, 116.13, 119.13, 125.49, 126.88 136.45, 139.87, 142.00, 167.82 (C=O). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76%. Found: C, 63.71; H, 6.34; N, 6.72.

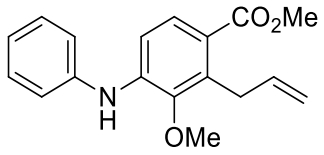
4.6 *Synthesis of Methyl 2-allyl-4-amino-3-methoxybenzoate (9)*



In a solution of **8** (0.2 g, 0.97 mmol) in DMF (5 mL) was added K_2CO_3 (0.27 g, 1.93 mmol) and after being stirred for 30 minutes at room temperature, iodomethane (0.1 mL, 1.45 mmol) was added and the reaction mixture was further stirred for 1 h at room temperature. The mixture was diluted with water (30 mL) and then extracted with ethyl ether (2 x 15 mL). The combined organic layers was washed with water (10 mL) and brine (10 mL) and then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Column chromatography of the light yellow oily material on silica gel eluting with petroleum ether-ethyl acetate (9:1) gave the title compound **9** as a dark pink crystalline solid. Yield: 0.16 g, 76%; m.p. 89-90 ^oC; IR (neat): 3505, 3374, 3026, 2938, 1687, 1612, 1427, 1335, 1261, 1029 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.75 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.85 (d, *J* = 5.8 Hz, 2H, Ar*CH*$_2$CH=CH$_2$), 4.95-5.00 (m, 2H, ArCH$_2$CH=*CH*$_2$), 6.05 (m, 1H, ArCH$_2$*CH*=CH$_2$), 6.62 (d, *J* = 8.2 Hz, 1H, H-5), 7.64 (d, *J* = 8.2 Hz, 1H, H-6); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 30.73 (Ar*CH*$_2$CH=CH$_2$), 51.47 (OCH_3), 59.92 (OCH_3), 112.59, 114.52, 119.49, 128.60, 135.98 137.88, 143.89, 145.10, 167.42 (C=O).

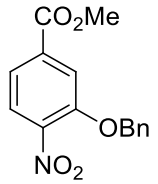
Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33%. Found: C, 65.10; H, 6.86; N, 6.28.

4.7 *Synthesis of Methyl 2-allyl-3-methoxy-4-(phenylamino)benzoate (10)*



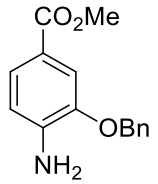
To a solution of compound **9** (0.25 g, 1.12 mmol) in dry CH_2Cl_2 (15 mL) was added phenyllead triacetate (0.67 g, 1.47 mmol) followed by the addition of copper(II) acetate (0.04 g, 0.22 mmol) and the reaction was stirred at room temperature for 24 h until the reaction was completed (TLC analysis). The mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure. The residues was resolved on silica column, eluting with petroleum ether-ethyl acetate (9:1) to get the title compound **10** as a pale yellow oil. Yield: 0.22 g, 66%; IR (neat): 3345, 3075, 2996, 1707, 1588, 1497, 1430, 1254, 1135, 1036 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.91 (d, J = 5.6 Hz, 2H, Ar*CH*$_2$CH=CH$_2$), 5.00-5.04 (m, 2H, ArCH$_2$CH=*CH*$_2$), 6.07 (m, 1H, ArCH$_2$*CH*=CH$_2$), 6.47 (br. s, 1H, NH), 7.09 (t, J = 5.6 Hz, 1H, Ar-H), 7.14 (d, J = 8.6 Hz, 1H, Ar-H), 7.22 (d, J = 8.4 Hz, 2H, Ar-H), 7.36 (m, 2H, Ar-H), 7.68 (d, J = 8.6 Hz, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 30.90 (Ar*CH*$_2$CH=CH$_2$), 51.54 (OCH_3), 60.65 (OCH_3), 110.70, 114.67, 120.54, 120.64, 122.99, 126.04, 128.33, 128.39, 129.46, 135.72, 137.78, 140.71, 141.06, 146.21, 167.32 (C=O). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71%. Found: C, 72.66; H, 6.49; N, 4.65.

4.8 *Synthesis of methyl 3-(benzyloxy)-4-nitrobenzoate (12)*



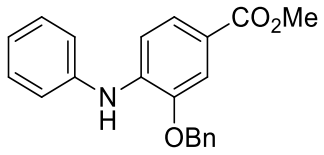
Potassium carbonate (0.9 g, 6.59 mmol) and benzylbromide (0.8 mL, 6.59 mmol) were sequencially added to a solution of methyl 3-hydroxy-4-nitrobenzoate (**5**) (1.0 g, 5.07 mmol) in acetone (31 mL). The suspension was heated under reflux for 6 h and then water was added. The aqueous layer was extracted with ethyl acetate (15 mL x 4). The combined organic layers were washed with brine (10 mL x 2), dried over Na_2SO_4 and evaporated under vacuum. Purification of the residue by flash chromatography on silica gel (petroleum ether-ethyl acetate, 4:1) afforded compound **12** as light yellow crystals, in quantitative yield. m.p. 92-94 ^oC; IR (neat) 3116, 3085, 3059, 3035, 2960 , 2879, 2837, 1727, 1602, 1524, 1495, 1437, 1421, 1374, 1372, 1294, 1266, 1232, 1213, 1188, 1113, 1080 cm^{-1}; ^1H-NMR (500 MHz, $CDCl_3$): δ 3.97 (s, 3H), 5.29 (s, 2H), 7.35 (t, J = 7.3 Hz, 1H), 7.40 (t, J = 7.3 Hz, 2H), 7.47 (d, J = 7.4 Hz, 2H), 7.71 (dd, J = 8.2, 1.4 Hz, 1H), 7.84 (d, J = 1.4 Hz, 1H), 7.84 Hz (d, J = 8.2 Hz, 1H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 52.85, 71.41, 116.10, 121.72, 125.38, 127.18, 128.44, 128.77, 134.80, 135.04, 142.88, 151.44, 165.17.

4.9 *Synthesis of methyl 4-amino-3-(benzyloxy)benzoate (13)*



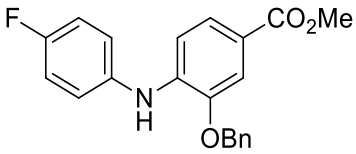
To a suspension of **12** (0.3 g, 1.26 mmol) in a mixture of glacial acetic acid (3 mL), ethanol (3 mL) and water (1.5 mL) was added reduced iron powder (0.36 g, 6.57 mmol). The resulting suspension was exposed to ultrasonic irradiation for 3 h at 30 °C with TLC analysis monitoring for the completion of the reaction. The reaction mixture was filtered to remove the iron residue which was washed with ethyl acetate (30 mL). The filtrate was partitioned with 2M KOH and the basic layer was further extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL) and water (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was then subjected to flash silica gel column chromatography (20% ethyl acetate in hexanes) yielding **13** (0.235g, 90%) as colorless crystalline solid, yield: 1.21 g (100%), m.p. 98-99 ^oC; IR (neat) 3493, 3387, 3005, 2945, 2872, 1693, 1605, 1515, 1452, 1428, 1384, 1361, 1295, 1259, 1208, 1136, 1101, 1007 cm^{-1}; ^1H-NMR (500 MHz, $CDCl_3$): δ 3.88 (s, 3H), 4.39 (br s, 2H), 5.08 (s, 2H), 6.69 (d, J = 7.9 Hz, 1H), 7.36 (t, J = 6.7Hz, 1H), 7.41 (t, J = 7.0 Hz, 2H), 7.45 (d, J = 6.7 Hz, 2H), 7.61 (d, J = 1H), 7.61 (d, J = 8.2, Hz, 1H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 51.63, 70.38, 112.55, 113.21, 119.04, 124.40, 127.76, 128.13, 128.55, 136.61, 141.64, 145.14, 167.28.

4.10 *Synthesis of Methyl 3-(benzyloxy)-4-(phenylamino)benzoate (14)*



Following the same procedure adopted for the synthesis of **10**, the reaction of compound **13** with phenyllead triacetate gave the title compound **14** as colorless crystalline solid. Yield: 0.26 g, 67%; m.p. 119-120 ºC; IR (neat): 3399, 3024, 2946, 1692, 1587, 1515, 1493, 1440, 1418, 1380, 1347, 1268, 1221, 1101 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.90 (s, 3H, OCH_3), 5.19 (s, 2H, O*CH*$_2$Ph), 6.56 (br. s, 1H, NH), 7.08 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.21-7.24 (m, 3H, Ar-H), 7.33-7.36 (m, 2H, Ar-H), 7.39 (m, 1H, Ar-H), 7.42-7.45 (m, 2H, Ar-H), 7.48 (d, *J* = 7.0 Hz, 1H, Ar-H), 7.62 (dd, *J* = 1.8, 8.2 Hz, 1H, Ar-H), 7.65 (d, *J* = 1.6 Hz, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 51.81 (OCH_3), 70.90 (O*CH*$_2$Ph), 111.02, 112.46, 115.35, 119.85, 120.36, 121.14, 123.19, 124.19, 127.96, 128.37, 128.71, 129.41. 129.57, 136.34, 138.64 140.53, 145.68, 156.03, 167.18 (C=O). Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20%. Found: C, 75.61; H, 5.78; N, 4.15.

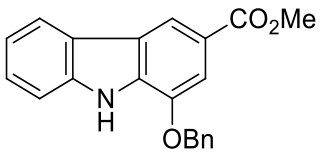
4.11 *Synthesis of Methyl 3-(benzyloxy)-4-((4 fluorophenyl)amino)benzoate (15)*



Following the same procedure adopted for the synthesis of **10**, the reaction of compound **13** with 4-fluorophenyllead triacetate gave the title compound **15** as a brown thick oil. Yield: 0.29 g, 70%; IR (neat): 3408, 3033, 2947, 1890, 1706, 1593, 1559, 1525, 1501, 1432, 1351, 1268, 1204, 1155, 1124, 1097 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.88

(s, 3H, OCH_3), 5.17 (s, 2H, O*CH*$_2$Ph), 6.44 (br. s, 1H, NH), 7.01-7.05 (m, 3H, Ar-H), 7.11-7.17 (m, 2H, Ar-H), 7.38-7.49 (m, 5H, Ar-H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.62 (dd, *J* = 1.8, 8.2 Hz, 1H, Ar-H), 7.65 (d, *J* = 1.6 Hz, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 51.79 (OCH_3), 70.89 (O*CH*$_2$Ph), 110.38, 112.38, 116.02, 116.21, 119.73, 123.86, 124.24, 128.03, 128.41, 128.72, 136.29, 136.40 139.27, 145.41, 159.19 (d, *J* = 243.0 Hz, C-6), 167.11 (C=O). Anal. Calcd for $C_{21}H_{18}FNO_3$: C, 71.78; H, 5.16; N, 3.99%. Found: C, 71.73; H, 5.19; N, 3.93.

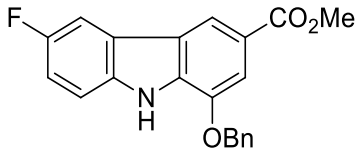
4.12 *Synthesis of methyl 1-(benzyloxy)-9H-carbazole-3-carboxylate (16)*



Under nitrogen atmosphere, to a solution of **14** (0.95 g, 2.85 mmol) in glacial acetic acid (60 mL) was added palladium(II) acetate (1.3 g, 5.7 mmol) and the mixture was heated at 100 ºC for 24 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel, eluting with petroleum ether-ethyl acetate (80:20) to afford **16** as a colorless crystalline solid. Yield: 0.5 g, 55%; m.p. 149-150 ºC; IR (neat): 3358, 3032, 2946, 1678, 1629, 1583, 1495, 1406, 1344, 1309, 1230, 1149, 1092 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.99 (s, 3H, OCH_3), 5.31 (s, 2H, O*CH*$_2$Ph), 7.27 (m, 1H, Ar-H), 7.39 (d, *J* = 7.3 Hz, 1H, Ar-H), 7.42-7.47 (m, 4H, Ar-H), 7.53 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.72 (d, *J* = 1.6 Hz, 1H, Ar-H), 8.11 (d, *J* = 7.9 Hz, 1H, Ar-H), 8.51 (d, *J* = 1.6 Hz, 1H, Ar-H), 8.53 (br. s, 1H, NH); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 52.06 (OCH_3), 70.71 (O*CH*$_2$Ph), 107.86, 111.23, 116.48, 120.30, 120.77, 121.89, 123.75, 123.79, 126.41,

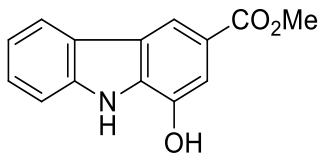
128.16, 128.44, 128.72, 136.44, 139.53, 144.29, 167.92 (C=O). Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23%. Found: C, 76.08; H, 5.21; N, 4.17.

4.13 *Synthesis of Methyl 1-(benzyloxy)-6-fluoro-9H-carbazole-3-carboxylate (17)*



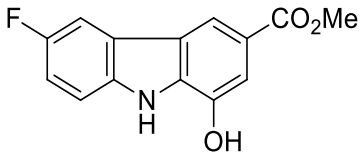
Following the same procedure adopted for the synthesis of **16**, the cyclodehydrogenation of compound **15** in acetic acid gave the title compound **17** as a colorless solid. Yield: 0.09 g, 59%; m.p. 172-176 ^{o}C; IR (neat): 3325, 2939, 1687, 1608, 1582, 1480, 1455, 1433, 1407, 1325, 1300, 1275, 1249, 1167, 1095, 1017 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.97 (s, 3H, OCH_3), 5.27 (s, 2H, O*CH*$_2$Ph), 7.17 (td, *J* = 2.4, 9.1 Hz, 1H), 7.35-7.45 (m, 4H, Ar-H), 7.51 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.69 (d, *J* = 1.3, 1H, Ar-H), 7.72 (dd, *J* = 8.2, 1.6 Hz, 1H, Ar-H), 8.42 (d, *J* = 1.2, 1H, Ar-H), 8.51 (br. s, 1H, NH); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 52.11 (OCH_3), 70.69 (O*CH*$_2$Ph), 106.31, 106.50, 108.04, 111.81, 111.90, 114.23, 114.44, 116.58, 121.89, 123.39, 124.34, 128.16, 128.47, 128.73, 134.08, 135.78, 136.28, 144.36, 159.42 (d, *J* = 249.0 Hz, C-6), 167.76 (C=O). Anal. Calcd for $C_{21}H_{16}FNO_3$: C, 72.20; H, 4.62; N, 4.01%. Found: C, 72.17; H, 4.65; N, 3.96.

4.14 *Synthesis of Methyl 1-hydroxy-9H-carbazole-3-carboxylate (18)*



To a suspension of **16** (0.48 g, 1.44 mmol) in a mixture of THF (20 mL) and ethanol (20 mL) was added palladium on activated carbon (0.05 g, 10% wet basis) and the reaction mixture was subjected to hydrogenation in a Parr apparatus at 50 psi for 5 h. The mixture was filtered through a pad of celite, and the filtrate was concentrated under vacuum and loaded on a silica column, eluting petroleum ether-ethyl acetate (2:1) afforded **15** as a white solid. Yield: 0.32 g, 91%. The spectral data of **18** matched with those of earlier values [23].

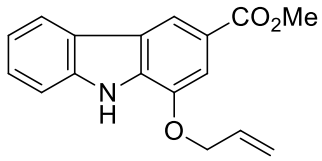
4.15 *Synthesis of Methyl 6-fluoro-1-hydroxy-9H-carbazole-3-carboxylate (19)*



Following the same procedure adopted for the synthesis of **18**, the title compound **19** was obtained as a white solid from the O-debenzylation of **17**. Yield: 0.2 g, 95%; m.p. 220-221; IR (neat): 3388, 3078, 2952, 1711, 1664, 1634, 1496, 1292, 1252, 1169 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.91 (s, 3H, OCH_3), 7.31 (td, J = 1.6, 8.8 Hz, 1H, Ar-H), 7.52 (d, J = 1.3 Hz, 1H, Ar-H), 7.55 (dd, J = 4.2, 8.8 Hz, 1H, Ar-H), 8.10 (d, J = 7.9 Hz, 1H, Ar-H), 8.38 (d, J = 1.3 Hz, 1H, Ar-H), 10.35 (br. s, 1H, NH), 11.64 (s, 1H, OH); ^{13}C-NMR (125.7 MHz, DMSO-d_6): δ 51.75 (OCH_3), 106.33, 110.29, 112.56, 112.63, 113.72, 113.92, 114.63, 120.58, 123.10, 124.34, 136.63, 142.99, 159.12 (d, J = 247.0 Hz, C-6),

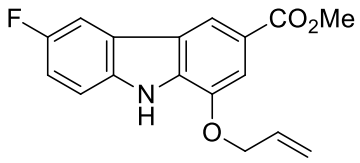
166.98 (C=O). Anal. Calcd for $C_{14}H_{10}FNO_3$: C, 64.86; H, 3.89; N, 5.40%. Found: C, 64.82; H, 3.94; N, 5.35.

4.16 *Synthesis of methyl 1-(allyloxy)-9H-carbazole-3-carboxylate (20)*



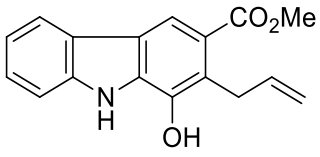
To a stirred solution of **18** (0.19 g, 0.79 mmol) in dry acetone (10 mL) was added K_2CO_3 (0.19 g, 1.34 mmol) and and the mixture was stirred for 20 min at room temperature. To the mixture was added NaI (0.12 g, 0.79 mmol) followed by the addition of allyl bromide (0.09 mL, 1.18 mmol) and the mixture was then stirred overnight at room temperature. After completion of the reaction (TLC analysis), the solvent was evaporated under reduced pressure. The residues were dissolved in ethyl acetate (20 mL) and successively washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (20% ethyl acetate in hexanes) to furnish **20** as a yellow solid. Yield 0.16 g, 72%; m.p. 175-178 ^oC; IR (neat): 3363, 2940, 2849, 1685, 1626, 1605, 1580, 1503, 1452, 1432, 1405, 1337, 1311, 1242, 1150, 1091, 1016 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.96 (s, 3H), 4.78 (d, J = 5.2 Hz, 2H), 5.35 (d, J = 10.7 Hz, 1H), 5.48 (d, J = 17.2 Hz, 1H), 6.13-6.19 (m, 1H), 7.27 (t, J = 6.7 Hz, 1H), 7.43-7.49 (m, 2H), 7.59 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 8.47 (s, 1H), 8.52 (br s, 1H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 52.04, 69.38, 107.84, 111.23, 116.35, 118.41, 120.28, 120.75, 121.84, 123.75, 126.40, 132.84, 133.05, 139.51, 145.97, 167.91.

4.17 *Synthesis of methyl 1-(allyloxy)-6-fluoro-9H-carbazole-3-carboxylate (21)*



Following the same procedure for the synthesis of **20**, the reaction of **19** (0.23 g, 0.88 mmol) with allyl bromide (0.13 mL, 1.51 mmol) gave the crude **21**, which was purified by column chromatography eluting with hexanes-ethyl acetate (5:1) to furnish **21** as an off white solid. Yield 0.23 g, 86%; m.p. 186-188 ^{o}C; IR (neat): 3318, 2945, 2920, 1681, 1609, 1581, 1505, 1478, 1457, 1437, 1327, 1300, 1279, 1250, 1165, 1095, 1021 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.98 (s, 3H), 4.80 (d, *J* = 5.5 Hz, 2H), 5.37 (dd, *J* = 10.7, 1.2 Hz, 1H), 5.39 (dd, *J* = 17.4, 1.5 Hz, 1H), 6.16 (m, 1H), 7.20 (td, *J* = 8.8, 2.4 Hz, 1H), 7.41 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.60 (d, *J* = Hz, 1H), 7.74 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.42 (s/d, 1H), 8.50 (br s, 1H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 52.08, 69.42, 106.33, 106.52, 108.11, 111.82, 111.89, 114.24, 114.43, 116.46, 118.50, 121.93, 132.74, 134.11, 135.80, 144.09, 167.73.

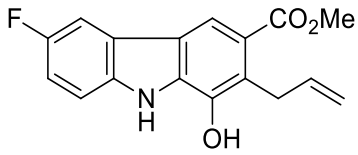
4.18 *Synthesis of methyl 2-allyl-1-hydroxy-9H-carbazole-3-carboxylate (22)*



In a microwave reaction vessel containing a solution of **20** (0.8 g, 2.84 mmol) in DMF (2 ml) was bubble nitrogen through the solution for 1 min and the vessel was placed inside CEM Discover S-Class microwave synthesizer where it was exposed to microwaves at

180ºC (260 W) for 2 h. After completion of the reaction, the mixture was diluted with ethyl acetate (20 mL) washed with water (5 mL) and then washed with brine (3 x 5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Column chromatography purifications of the yellow oily material, eluting with ethyl acetate-hexane (1:1) yielded compound **22** as pale solid. Yield 0.6 g, 75%; m.p. 135-138 ºC; IR (neat): 3335, 3056, 3028, 2983, 2942, 1709, 1658, 1606, 1495, 1422, 1356, 1306, 1273, 1095 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.94 (s, 3H), 4.02 (d, *J* = 5.8 Hz, 2H), 5.18 (d, *J* = 7 Hz, 1H), δ 5.20 (d, *J* = Hz, 1H), 5.69 (br s, 1H), 6.12-6.18 (m, 1H), 7.24-7.27 (m, 1H), 7.41-7.46 (m, 2H), 8.04 (d, *J* = 7.6 Hz, 1H), 8.37 (s, 1H), 8.48 (br s, 1H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 31.37, 51.96, 111.12, 115.37, 116.87, 119.96, 120.51, 121.76, 122.37, 122.50, 123.70, 126.15, 132.24, 137.23, 139.82, 140.37, 168.96.

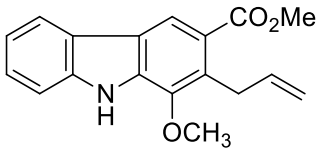
4.19 *Synthesis of methyl 2-allyl-6-fluoro-1-hydroxy-9H-carbazole-3-carboxylate (23)*



Following the same procedure adopted for the synthesis of compound **22**, the reaction of **21** (0.2 g, 0.66 mmol) in DMF (2 ml) in CEM Discover S-Class microwave synthesizer gave the product as a yellow oily material which was resolved on column chromatography, eluting with hexane-ethyl acetate (1:1) to afford compound **23** as a white solid. Yield 0.18 g, 90%; m.p .125-130 ºC; IR (neat): 3383, 2922, 2851, 2155, 1996, 1843, 1708, 1661, 1609, 1494, 1453, 1433, 1347, 1288, 1253, 1220, 1166, 1031 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-

d_6): δ 3.80 (s, 3H), 3.89 (d, J = 5.8 Hz, 2H), 4.88-4.92 (m, 2H), 5.92 (m, 1H), 7.23 (td, J = 8.8, 2.1 Hz, 1H), 7.53 (dd, J = 8.5, 4.3 Hz, 1H), 7.95 (dd, J = 9.7, 2.1 Hz, 1H), 8.22 (s, 1H), 9.20 (br s, 1H), 11.09 (s, 1H); ^{13}C-NMR (125.7 MHz, DMSO-d_6): δ 29.87, 51.65, 105.93, 106.12, 112.53, 113.43, 113.63, 120.83, 121.54, 123.76, 134.08, 136.42, 137.61, 140.34, 168.16.

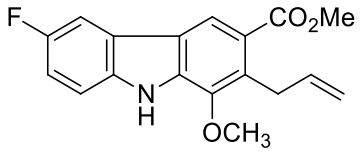
4.20 *Synthesis of methyl 2-allyl-1-methoxy-9H-carbazole-3-carboxylate (24)*



To a solution of **22** (0.25 g, 0.89 mmol) in DMF (5 mL) was added K_2CO_3 (0.15 g, 1.07 mmol) and after being stirred at room temperature for 30 min, CH_3I (0.07 mL, 1.07 mmol) was added to the mixture. The reaction was for 1 h at room temperature for 1 h and then diluted with water (30 mL) and extracted with ethyl ether (15 mL). The organic layer was successively washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Column chromatography of the light yellow material on silica gel eluting with ethyl acetate-hexanes (1:12) afforded **24** as white powder. Yield 0.19g, 73%; m.p. 98-100 ^oC; IR (neat): 3319, 2933, 2838, 2334, 1680, 1626, 1604, 1494, 1450, 1428, 1387, 1341, 1251, 1221, 1137, 1095, 1040 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.95 (s, 3H), 3.98 (s, 3H), δ 4.09 (d, J = 5.4 Hz, 2H), δ 5.00-5.06 (m, 2H), 6.15-6.20 (m, 1H), 7.27 (t, J = 6.4 Hz, 1H), 7.42-7.45 (m, 2H), 8.07 (d, J = 7.9 Hz, 1H), 8.58 (s, 1H), 8.81 (br s, 1H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 30.67, 51.94, 61.32, 111.18,

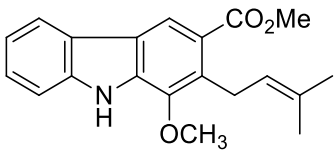
114.61, 120.22, 120.34, 120.46, 122.05, 122.90, 123.77, 126.37, 131.01, 135.55, 138.28, 139.94, 143.35, 168.59.

4.21 *Synthesis of methyl 2-allyl-6-fluoro-1-methoxy-9H-carbazole-3-carboxylate (25)*



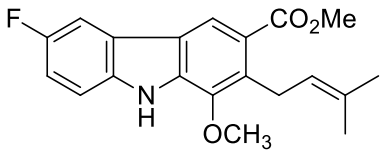
Following the same procedure adopted for the synthesis of compound **24**, the reaction of compound **23** (0.2 g, 0.66 mmol) with CH_3I (0.05 mL, 0.8 mmol) gave, after the work up, the crude product which was purified by column chromatography on silica gel with ethyl acetate-hexanes (1:12) to yield **25** as a white solid. Yield: 0.15 g, 71%; m.p. 130-132 ^oC; IR (neat): 3341, 3066, 2936, 2828, 1677, 1630, 1607, 1495, 1461, 1438, 1386, 1326, 1281, 1233, 1190, 1166, 1043, cm^{-1}; ^1H-NMR (500 MHz, $CDCL_3$): δ 3.93 (s, 3H), 3.97 (s, 3H), 4.02 (d, *J* = 5.8 Hz, 2H), 4.96 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.01 (dd, *J* = 10.5, 1.5 Hz, 1H), 6.11 (m, 1H), 7.19 (td, *J* = 8.8, 2.1 Hz, 1H), 7.41 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.72 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.28 (br s, 1H), 8.46 (s, 1H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 30.66, 51.95, 61.44, 106.28, 106.47, 111.71, 111.76, 114.17, 114.38, 114.69, 120.49, 122.52, 122.59, 124.65, 131.72, 136.08, 136.56, 138.09, 143.53, 168.15.

4.22 *Synthesis of Methyl 1-methoxy-2-(3-methylbut-2-en-1-yl)-9H-carbazole-3-carboxylate (26)*



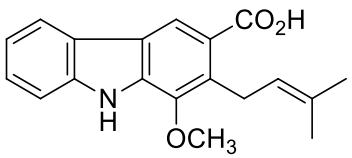
To a solution of compound **24** (0.19 g, 0.64 mmol) in anhydrous dichloromethane (20 ml) was added successively 2-methyl-2-butene (3.5 ml) and Grubbs' second generation catalyst (0.016 g, 0.02 mmol) under nitrogen atmosphere. The solution was stirred for 24 h at room temperature and concentrated under vacuum. Column chromatography of the dark brown oily material, eluting with ethyl acetate-hexane (1:6) gave compound **26** as colorless crystalline solid. Yield: 0.19 g, 91%; m.p. 129-133 ^{o}C; IR (neat): 3334, 2936, 1707, 1685, 1626, 1605, 1568, 1494, 1430, 1389, 1342, 1242, 1097 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.69 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 3.91-3.96 (m, 8H, 2 x OCH_3, Ar*CH*$_2$-), 5.24 (m, 1H, $ArCH_2$*CH*=$C(CH_3)_2$), 7.25 (m, 1H, Ar-H), 7.42-7.45 (m, 2H, Ar-H), 8.07 (d, *J* = 7.9 Hz, 1H, Ar-H), 8.58 (br. s, 1H, NH), 8.46 (s, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 18.10 (CH_3), 25.74 (CH_3), 25.96 (CH_2), 51.96 (OCH_3), 61.08 (OCH_3), 111.12, 120.16, 120.20, 120.46, 122.37, 122.66, 123.91, 124.19, 126.28, 131.28, 133.21, 135.57, 139.95, 143.22, 168.80 (C=O). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33%. Found: C, 74.23; H, 6.60; N, 4.27.

4.23 *Synthesis of Methyl 6-fluoro-1-methoxy-2-(3-methylbut-2-en-1-yl)-9H-carbazole-3-carboxylate (27)*



Following the same procedure adopted for the synthesis of **26**, the title compound **27** was obtained as a white solid. Yield: 0.15 g, 84%; m.p. 115-116 ^{o}C; IR (neat): 3395, 2967, 1692, 1631, 1609, 1587, 1485, 1434, 1377, 1345, 1320, 1274, 1230, 1187, 1167, 1040 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.69 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 3.91-3.96 (m, 8H, 2 x OCH_3, Ar*CH*$_2$-), 5.22 (m, 1H, $ArCH_2$*CH*=$C(CH_3)_2$), 7.17 (td, *J* = 2.4, 8.8 Hz, 1H, Ar-H), 7.37 (dd, *J* = 4.2, 8.8 Hz, 1H, Ar-H), 7.68 (dd, *J* = 2.4, 8.8 Hz, 1H, Ar-H), 8.25 (br. s, 1H, NH), 8.40 (s, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 18.12 (CH_3), 25.77 (CH_3), 25.94 (CH_2), 52.00 (OCH_3), 61.17 (OCH_3), 106.35 (d, *J* = 24.9), 111.66 (d, *J* = 9.3), 114.13 (d, *J* = 24.9), 120.33, 122.28, 122.68, 123.93, 124.61, 124.68, 131.52, 133.81, 136.07, 136.55, 143.29, 157.89 (d, *J* = 236.5, C-6), 168.47 (C=O). Anal. Calcd for $C_{20}H_{20}FNO_3$: C, 70.37; H, 5.91; N, 4.10%. Found: C, 70.33; H, 5.95; N, 4.06.

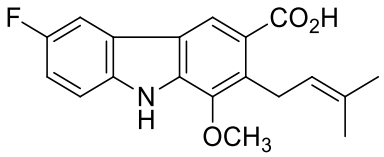
4.24 *Synthesis of 1-Methoxy-2-(3-methylbut-2-en-1-yl)-9H-carbazole-3-carboxylic acid (28)*



To a solution of **26** (0.01 g, 0.30 mmol) in a mixture of MeOH (2 mL) and THF (1 mL) was added a solution of KOH (15 mL, 30% in H_2O) and the mixture was heated

overnight at 50 ºC. The reaction was cooled to room temperature, acidified to pH 4 with 2M HCl and then extracted with ethyl acetate (2 x 30 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was passed through a pad of silica, eluting with hexanes-ethyl acetate (1:1) to afford compound **28** as a white crystalline solid. Yield: 80%, m.p. 176-177 ºC; IR (neat): 3337, 3062, 2925, 1675, 1610, 1448, 1406, 1278, 1236, 1031 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD): δ 1.57 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 3.85 (d, *J* = 5.5 Hz, 1H, Ar*CH*$_2$-), 5.14 (m, 1H, ArCH$_2$*CH*=C(CH$_3$)$_2$), 7.08 (td, *J* = 1.1, 7.9 Hz, 1H, Ar-H), 7.28 (td, *J* = 1.2, 7.3 Hz, 1H, Ar-H), 7.39 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.93 (d, *J* = 7.9 Hz, 1H, Ar-H), 8.37 (s, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, CD_3OD): δ 18.20 (CH_3), 25.94 (CH_3), 26.65 (CH_2), 61.35 (OCH_3), 120.62, 120.95, 121.00, 123.13, 123.73, 124.79, 125.65, 127.08, 131.50, 133.87, 137.05, 142.10, 144.72, 172.09 (C=O). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53%. Found: C, 73.72; H, 6.24; N, 4.48.

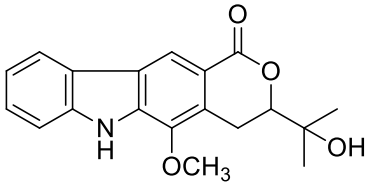
4.25 *Synthesis of 6-Fluoro-1-methoxy-2-(3-methylbut-2-en-1-yl)-9H-carbazole-3-carboxylic acid (29)*



Following the same procedure adopted for the synthesis of **28**, the basic hydrolysis of **27** gave the title compound **29** as a white crystalline solid from. Yield: 0.084 g, 77%; m.p. 196-197 ºC; IR (neat): 3455, 3040, 2913, 1664, 1634, 1612, 1588, 1569, 1489, 1443, 1376, 1342, 1317, 1277, 1243, 1192, 1170, 1098 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD): δ 1.65 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 3.91-3.96 (s, 5H, OCH_3, Ar*CH*$_2$-), 5.22 (m, 1H,

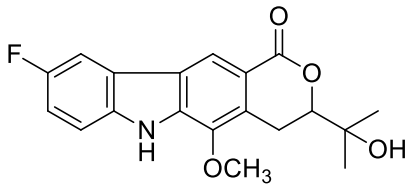
$ArCH_2CH$=$C(CH_3)_2$), 7.14 (td, J = 2.4, 8.8 Hz, 1H, Ar-H), 7.43 (dd, J = 4.3, 8.8 Hz, 1H, Ar-H), 7.70 (dd, J = 2.4, 8.8 Hz, 1H, Ar-H), 8.45 (s, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, CD_3OD): δ 18.19 (CH_3), 25.92 (CH_3), 26.66 (CH_2), 61.35 (OCH_3), 106.53 (d, J = 23.86), 113.05 (d, J = 9.34), 114.64 (d, J = 25.93), 121.28, 123.29, 125.34, 125.42, 125.79, 131.63, 134.35, 138.10, 138.41, 144.79, 158.96 (d, J = 234.47, C-6), 171.92 (C=O). Anal. Calcd for $C_{19}H_{18}FNO_3$: C, 69.71; H, 5.54; N, 4.28%. Found: C, 69.67; H, 5.58; N, 4.22.

4.26 *Synthesis of 3-(2-Hydroxypropan-2-yl)-5-methoxy-3,4-dihydropyrano[4,3-b]carbazol-1(6H)-one (1)*



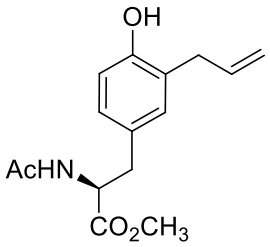
To an ice-cold solution of **28** (0.03 g, 0.08 mmol) in anhydrous CH_2Cl_2 (5 mL) was added *m*-CPBA (0.02 g, 0.12 mmol) and the reaction was stirred for 2 h at room temperature. After the completion of reaction (TLC analysis) the solvent was evaporated under vacuum and residue was diluted with H_2O (5 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 x 6 mL) followed by water (6 mL) and brine (6 mL). The organic phase was dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by silica column, eluting with hexanes-ethyl acetate (1:1) to get the title compound **1** as a light brown solid. Yield: 0.02 g, 78%. All the spectral data of **1** matched with those of natural mafaicheenamine A [12].

4.27 *Synthesis of 9-Fluoro-3-(2-hydroxypropan-2-yl)-5-methoxy-3,4-dihydropyrano[4,3-b]carbazol-1(6H)-one (2)*



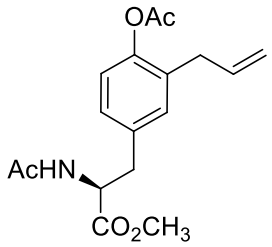
Following the same procedure adopted for the synthesis of **1**, the oxidative cyclization of **29** gave the title compound **2** as a white crystalline solid from. Yield: 0.036 g, 80%; m.p. 276-277 ºC; IR (neat): 3506, 3218, 2989, 2971, 2933, 1691, 1634, 1612, 1584, 1506, 1482, 1385, 1362, 1323, 1293, 1265, 1240, 1216, 1166, 1121, 1080, 1045 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD): δ 1.38 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 3.00 (dd, *J* = 12.8, 16.4 Hz, 1H, H-1'b), 3.45 (dd, *J* = 16.4, 2.7 Hz, 1H, H-1'a), 3.98 (s, 3H, OCH_3), 4.29 (dd, *J* = 2.7, 12.8 Hz, 1H, H-2'), 7.20 (dd, *J* = 6.4, 8.8 Hz, 1H, Ar-H), 7.48 (dd, *J* = 4.3, 8.8 Hz, 1H, Ar-H), 7.80 (dd, *J* = 2.4, 8.8 Hz, 1H, Ar-H), 8.55 (s, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, CD_3OD): δ 21.96 (C-1'), 23.69 (CH_3), 24.94 (CH_3), 59.99 (OCH_3), 70.41 (C-3'), 84.53 (C-2'), 105.55 (d, *J* = 24.9), 111.94 (d, *J* = 9.3), 113.98 (d, *J* = 26.0), 115.65, 119.32, 123.66, 123.86 (d, *J* = 9.3), 123.89, 128.53, 137.06, 137.84, 141.09, 157.79 (d, *J* = 235.5, C-6), 167.49 (C=O). Anal. Calcd for $C_{19}H_{18}FNO_4$: C, 66.46; H, 5.28; N, 4.08%. Found: C, 66.40; H, 5.33; N, 4.03.

4.28 *(S)-methyl 2-acetamido-3-(3-allyl-4-hydroxyphenyl)propanoate (34)*



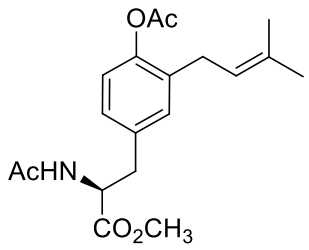
To a microwave reaction vessel containing a solution of aryl ether **33** (0.75 g, 2.70 mmol) in N,N-dimethylaniline (4 ml). After gentle bubbling nitrogen through the solution for 1 min, the vessel was placed inside CEM Discover S-Class microwave synthesizer where it was exposed to microwaves at 250 ºC (260 W) for 2 h. After completion of the reaction, the mixture was diluted with ethyl acetate (50 mL) and extracted with 3M hydrochloric acid (3 x 10 mL). The organic layer was washed successively with saturated sodium hydrogen carbonate (15 mL) and then brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. Column chromatography purifications of the yellow oily material, eluting with ethyl acetate-hexane (1:1) yielded compound **34** as a pale yellow solid. Yield: 0.56 g, 75%; m.p. 91-92 ºC; $[\alpha]_D^{25}$ +25.95 (c. 1.15, $CHCl_3$); IR (neat): 3418, 3300, 3081, 3006, 2956, 1717, 1662, 1510, 1432, 1209, 1121 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.92 (s, 3H, $NCOCH_3$), 2.96 (dd, 2H), 3.27 (m, 2H), 3.66 (s, 3H, OCH_3), 4.76 (m, 1H), 4.99-5.03 (m, 2H), 5.90 (m, 1H), 5.99 (d, 1H, J = 7.9 Hz, NH), 6.62 (m, 1H, aromatics), 6.72 (m, 2H, aromatics); ^{13}C-NMR ($CDCl_3$, 500 MHz): δ 23.05, 34.46, 37.05, 52.35, 53.31, 115.64, 116.07, 125.92, 127.26, 128.13, 131.04, 136.46, 153.39, 170.05, 172.29. Anal. calcd. for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.93; H, 6.94; N, 5.01.

4.29 *(S)-methyl 2-acetamido-3-(4-acetoxy-3-allylphenyl)propanoate (35)*



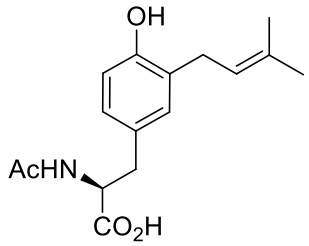
To a solution of compound **34** (0.5 g, 1.80 mmol) in anhydrous dichloromethane (15 mL) at 0 ºC was added triethylamine (0.75 ml, 5.41 mmol). After bring stirred for 10 minutes, acetic anhydride (0.35 ml, 3.60 mmol) was added dropwise and the reaction was stirred for 2 h at room temperature. The mixture was added ethyl acetate (30 mL) and washed successively with saturated sodium hydrogen carbonate (15 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum to obtain compound **35** as an off-white solid. Yield: 0.57 g, 99%; m.p. 104 ºC; $[\alpha]_D^{25}$ +56.6 (c. 1.0, $CHCl_3$); IR (neat): 3311, 3086, 2948, 1740, 1649, 1639, 1543, 1497, 1433, 1371, 1202, 1185, 1166 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.99 (s, 3H, $NCOCH_3$), 2.29 (s, 3H, $COCH_3$), 3.10 (t, 2H, *J* = 5.5 Hz), 3.25 (d, 2H, *J* = 6.7 Hz), 3.72 (s, 3H, OCH_3), 4.86 (m, 1H), 5.03-5.09 (m, 2H), 5.85 (m, 1H), 5.89 (d, 1H, *J* = 7.9 Hz, NH), 6.96 (m, 3H, aromatics); ^{13}C-NMR ($CDCl_3$, 500 MHz): δ 23.18, 29.71, 34.45, 37.16, 52.38, 53.06, 116.47, 122.47, 128.18, 131.23, 132.03, 133.70, 135.70, 148.01, 169.35, 169.61, 171.94. Anal. calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.90; H, 6.68; N, 4.32.

4.30 *(S)-methyl 2-acetamido-3-(4-acetoxy-3-(3-methylbut-2-en-1-yl)phenyl)propanoate (36)*



To a solution of compound **35** (0.23 g, 0.72 mmol) in anhydrous dichloromethane (36 ml) was added successively 2-methyl-2-butene (4 ml) and Grubbs' second generation catalyst (0.018 g, 0.021 mmol) under nitrogen atmosphere. The solution was stirred for 24 h at room temperature and concentrated under vacuum. Column chromatography of the dark brown oily material, eluting with ethyl acetate:hexane (2:3) gave compound **36** as a light yellow solid (0.21 g, 84%). Yield: 0.21 g, 84%; m.p. 81-82 ^{o}C; $[\alpha]_D^{25}$ -59.7 (c. 0.22, $CHCl_3$). IR (neat): 3288, 3061, 2951, 1735, 1649, 1539, 1492, 1370, 1185, 1164 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.69 (s, 3H), 1.74 (s, 3H), 1.99 (s, 3H, $NCOCH_3$), 2.30 (s, 3H, $COCH_3$), 3.10 (m, 2H), 3.25 (d, 2H, *J* = 7.3 Hz), 3.72 (s, 3H, OCH_3), 4.87 (m, 1H), 5.29 (m, 1H), 5.92 (d, 1H, *J* = 9.7 Hz, NH), 6.93 (m, 3H, aromatics); ^{13}C-NMR ($CDCl_3$, 500 MHz): δ 17.82, 23.14, 25.77, 28.59, 29.71, 37.15, 52.31, 53.03, 121.38, 122.31, 127.76, 130.83, 133.41, 133.61, 147.96, 169.41, 169.59, 171.96. Anal. calcd. for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.63; H, 7.30; N, 3.97.

4.31 *(S)-2-acetamido-3-(4-hydroxy-3-(3-methylbut-2-en-1-yl)phenyl)propanoic acid (3)*



To a solution of compound **8** (0.16 g, 0.46 mmol) in a mixture of tetrahydrofuran, methanol and water (10 ml, in 3:1:1 ratio) was added lithium hydroxide monohydrate (0.096 g, 2.3 mmol) and the mixture was stirred for 3 h at room temperature. The solvent was evaporated and residue was diluted with chloroform (20 ml) and washed with 1M hydrochloric acid (3 ml). The organic layer was dried over anhydrous Na_2SO_4, concentrated under vacuum and passed over a plug of silica, eluting with methanol-dichloromethane (0.5:9.5) to afford compound **1** as a colorless solid (0.09 g, 69%). The spectral data of **1** coincided with literature values [12].

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

The first total synthesis of tyrosine derivative **3** for its antitumoral activity was successfully achieved in overall high yielding sequence. The first total synthesis of anticancer natural product mafaicheenamine A **1** was accomplished. Substitution of aromatic and heteroaromatic rings with fluorine substituent is a common practice in drug discovery resulting in enhanced drug potency, target selectivity and drug metabolism. Therefore the fluoro analogue of **1** was synthesized. Our synthetic strategy also has led to the expedient route to realize an important naturally anticancer product clausine-E that is a common intermediate in the synthesis of other naturally occurring bioactive carbazole alkaloids. Our approach paved a way to synthesize clausine-E in overall yield of 34% from commercially available methyl 4-amino-3-(benzyloxy)benzoate (**18**). Similarly, the unnatural 6-Fluoro analogue of clausine was afforded from our synthetic sequence. The unnatural 6-Fluoromafaicheenamine A **2** and 6-Fluoroclausine can be screened for its potential pharmacological activities.

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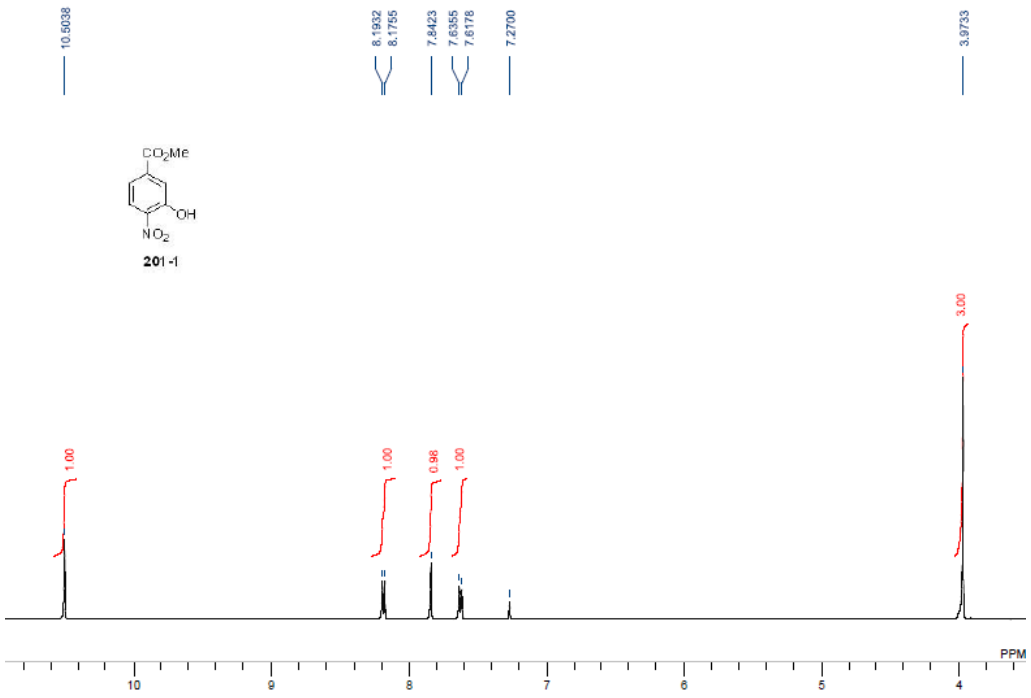
Appendix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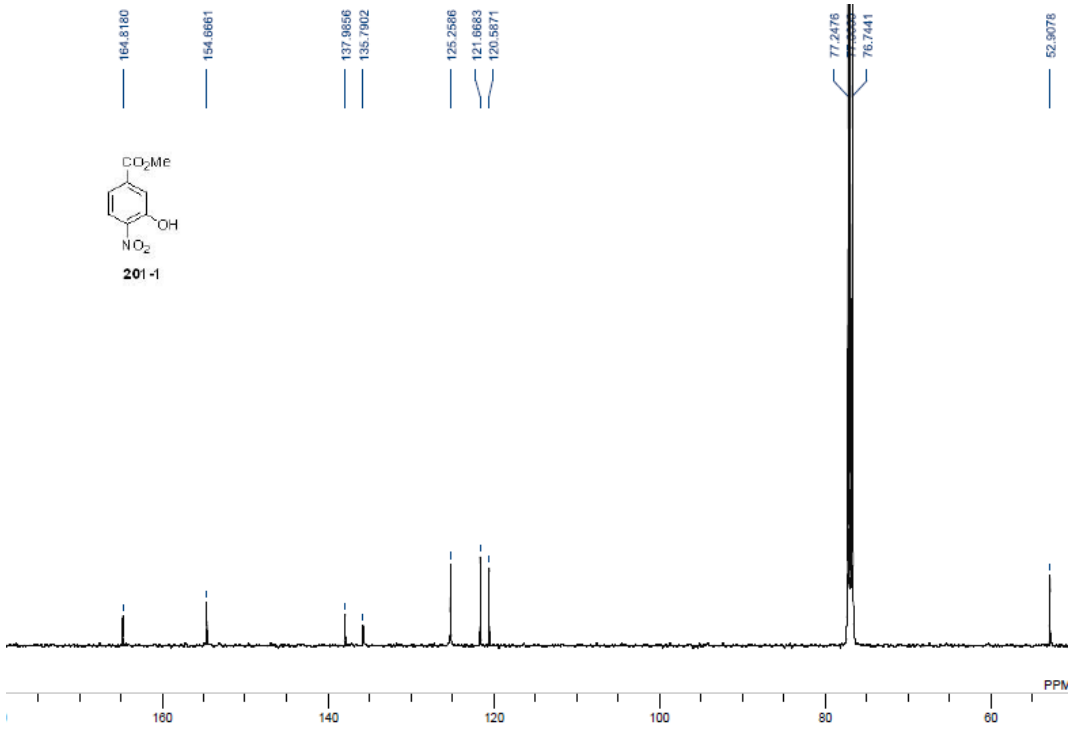
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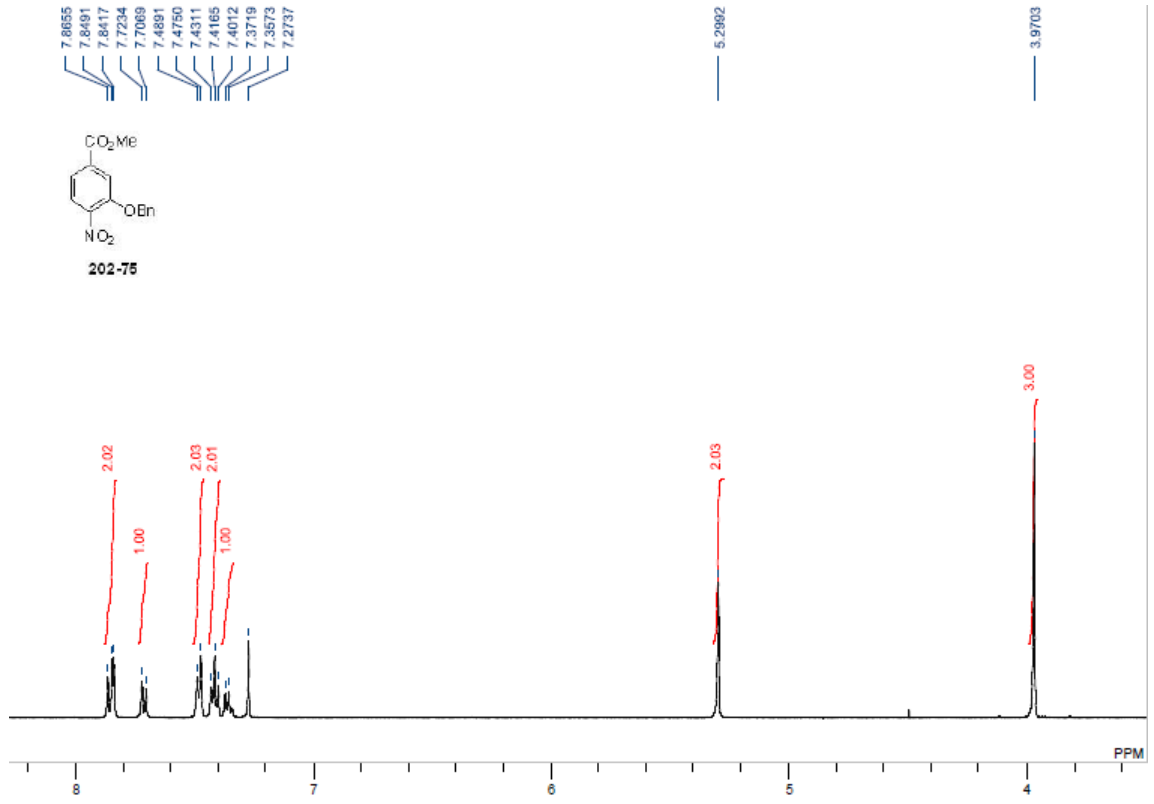
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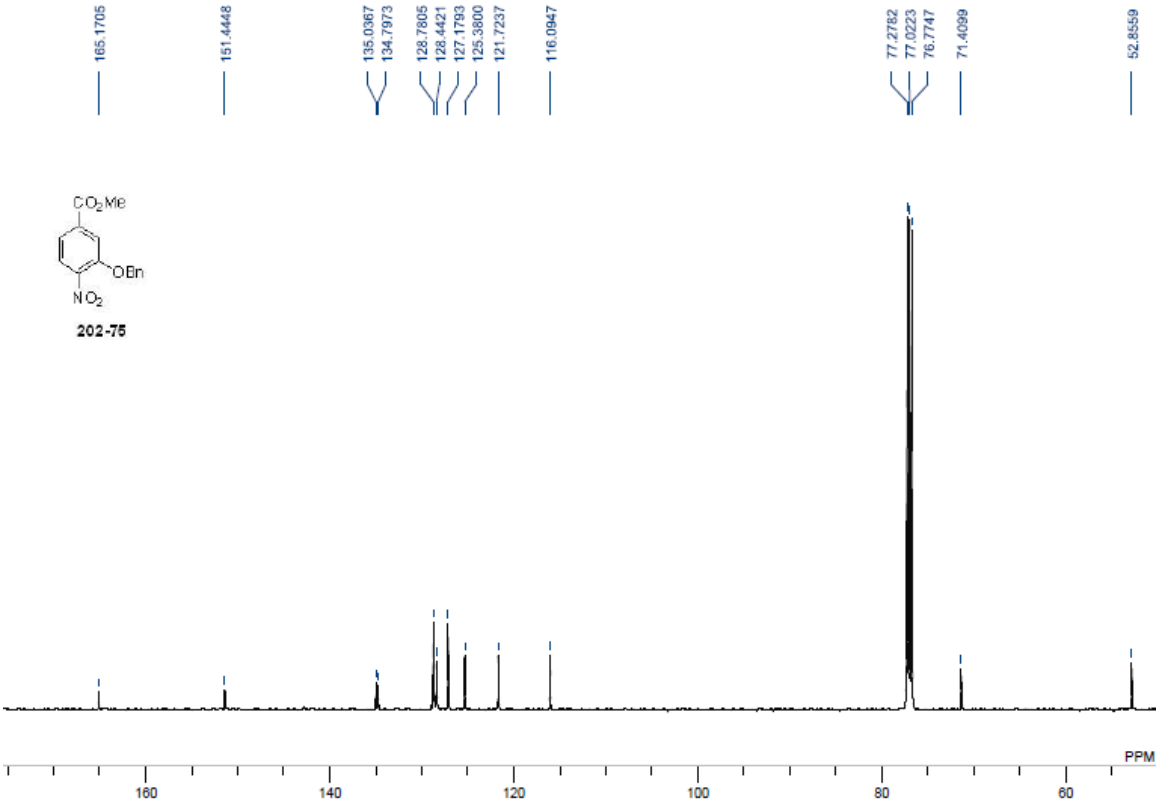
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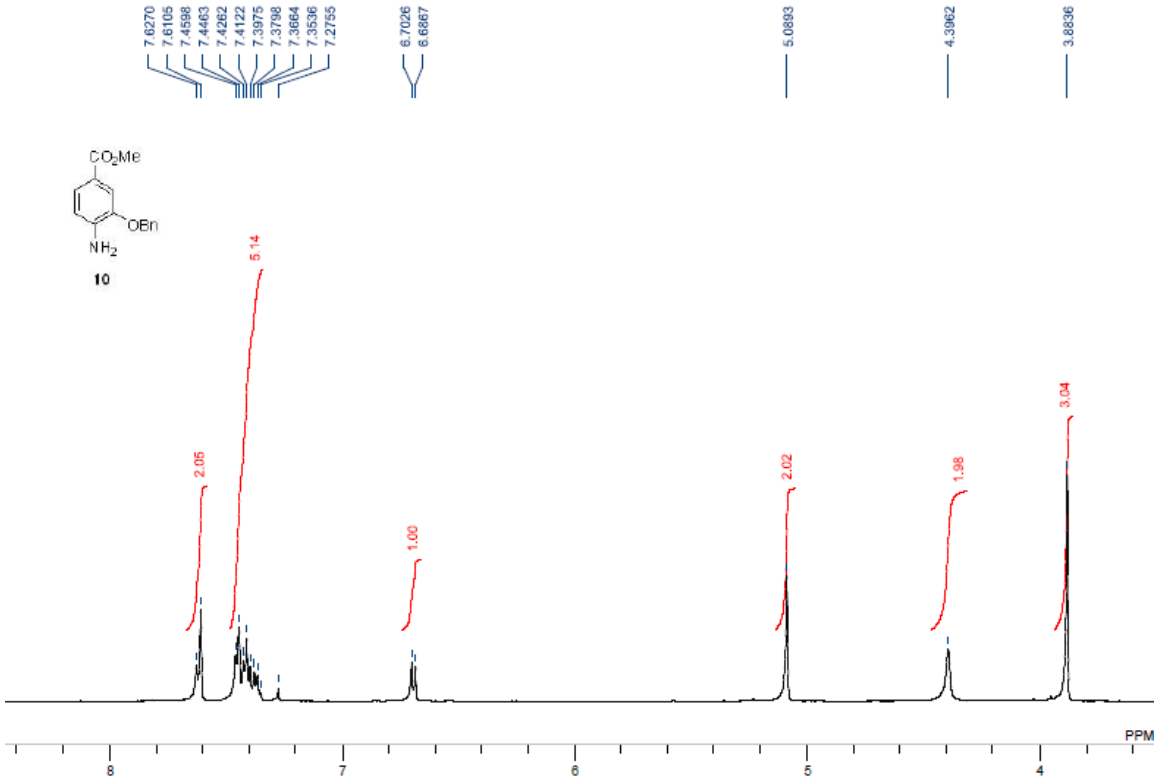
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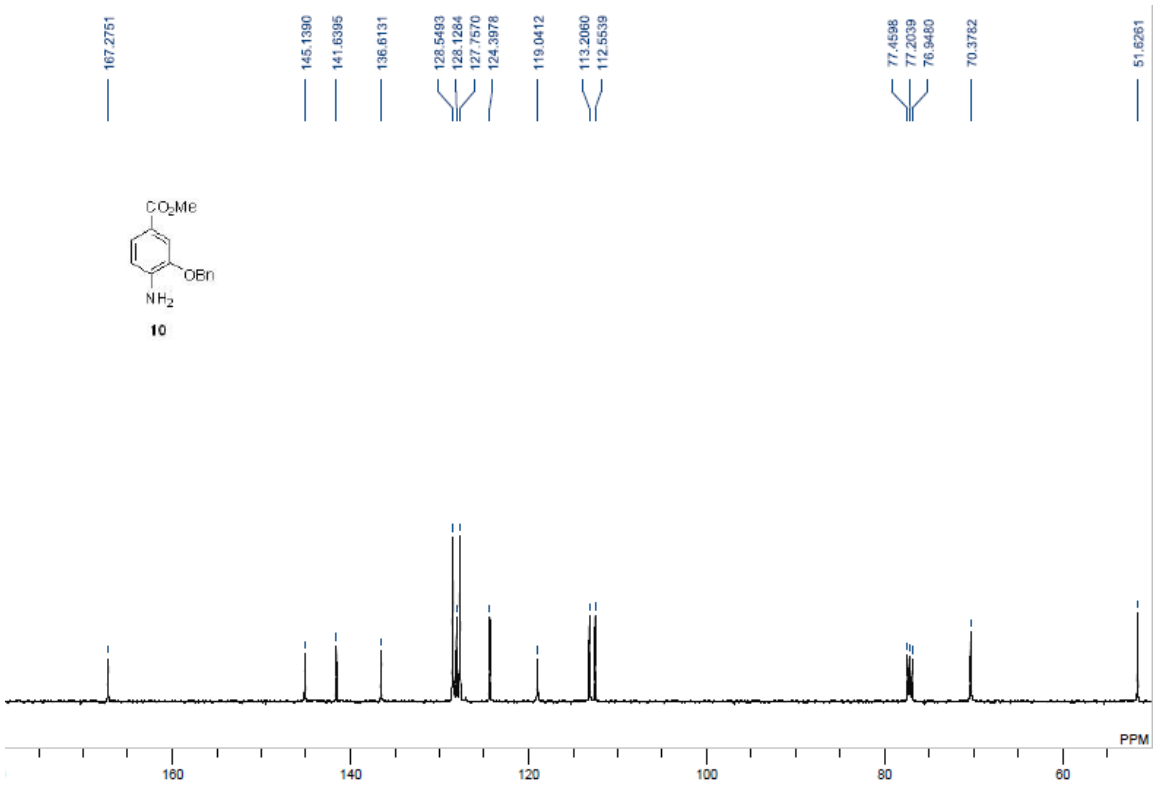
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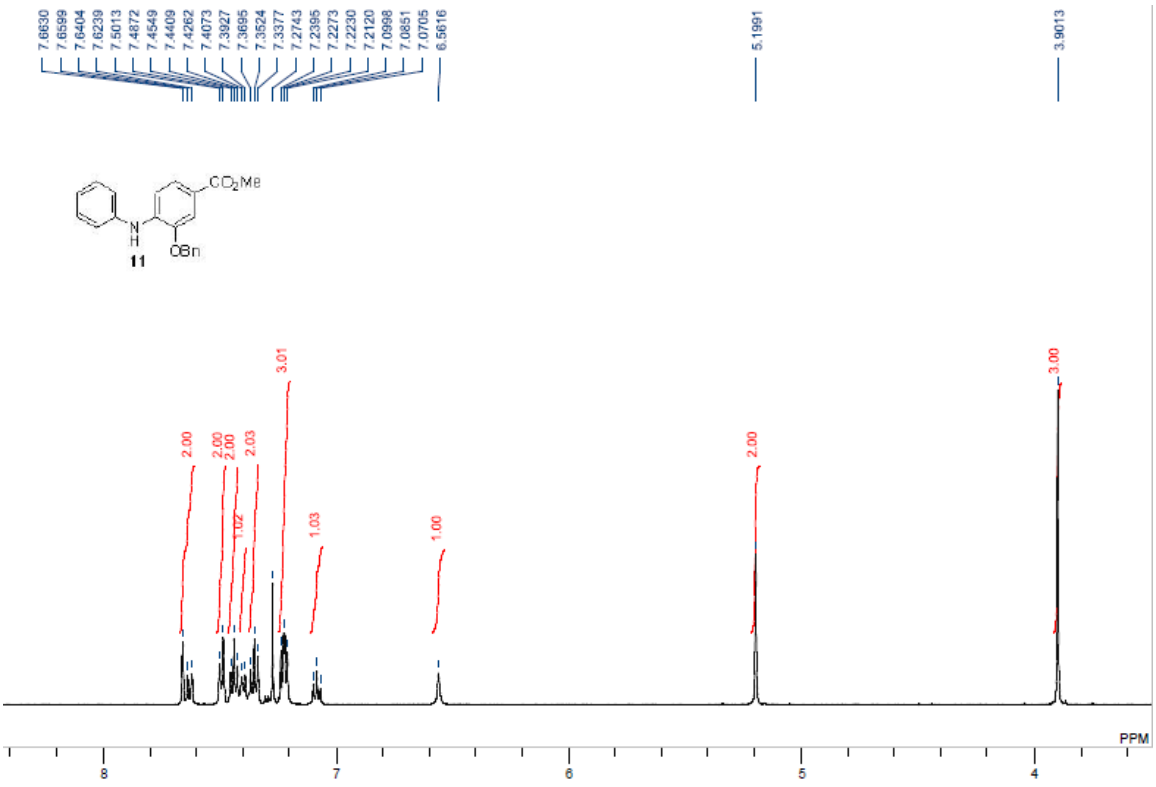
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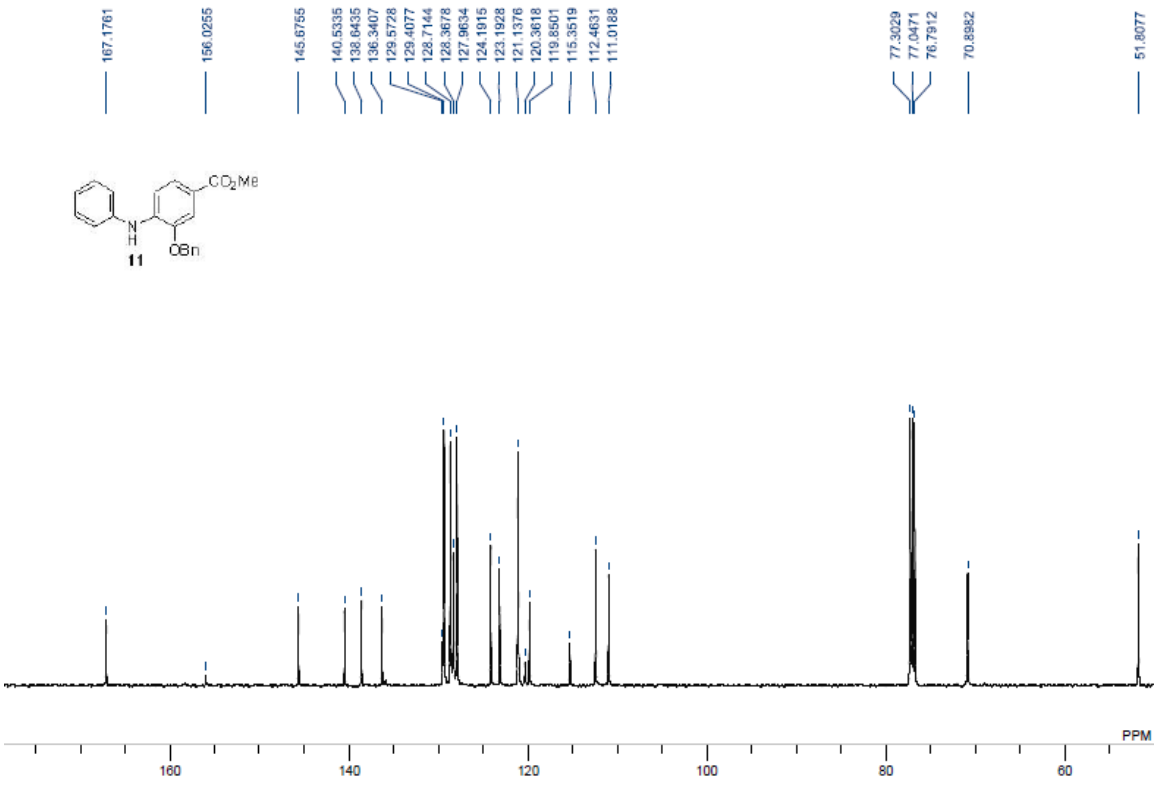
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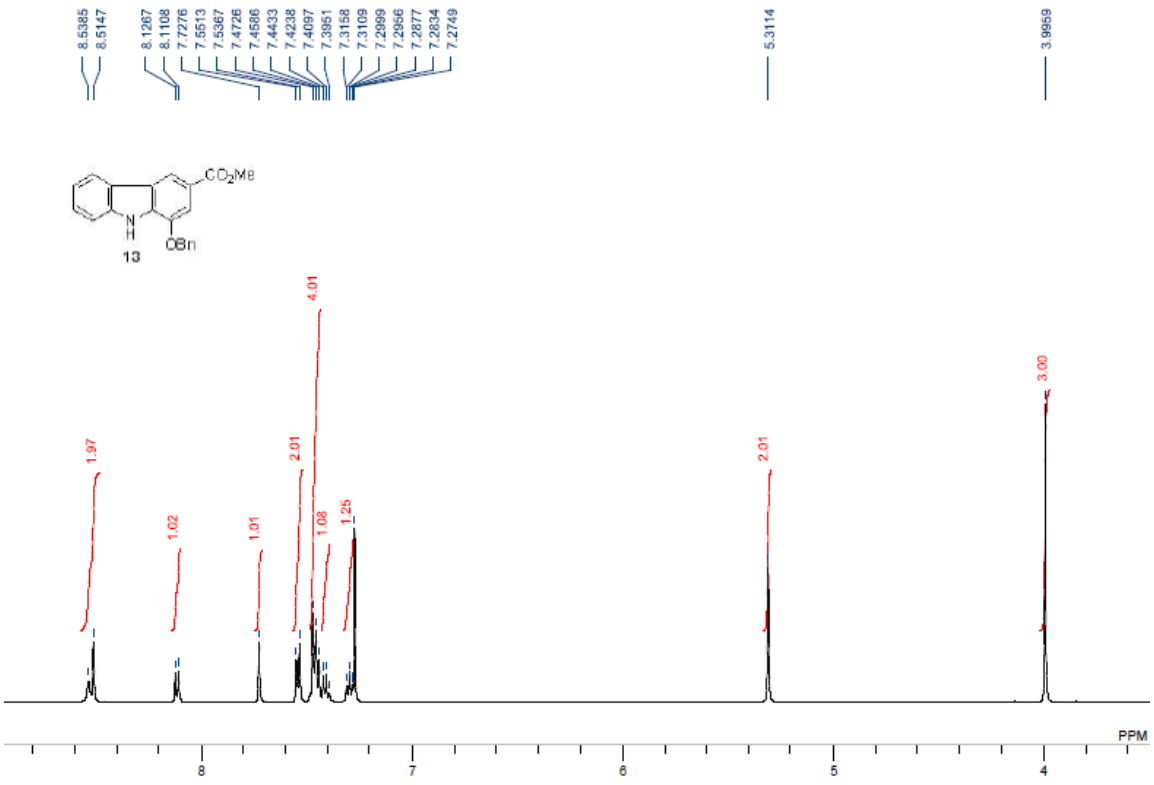
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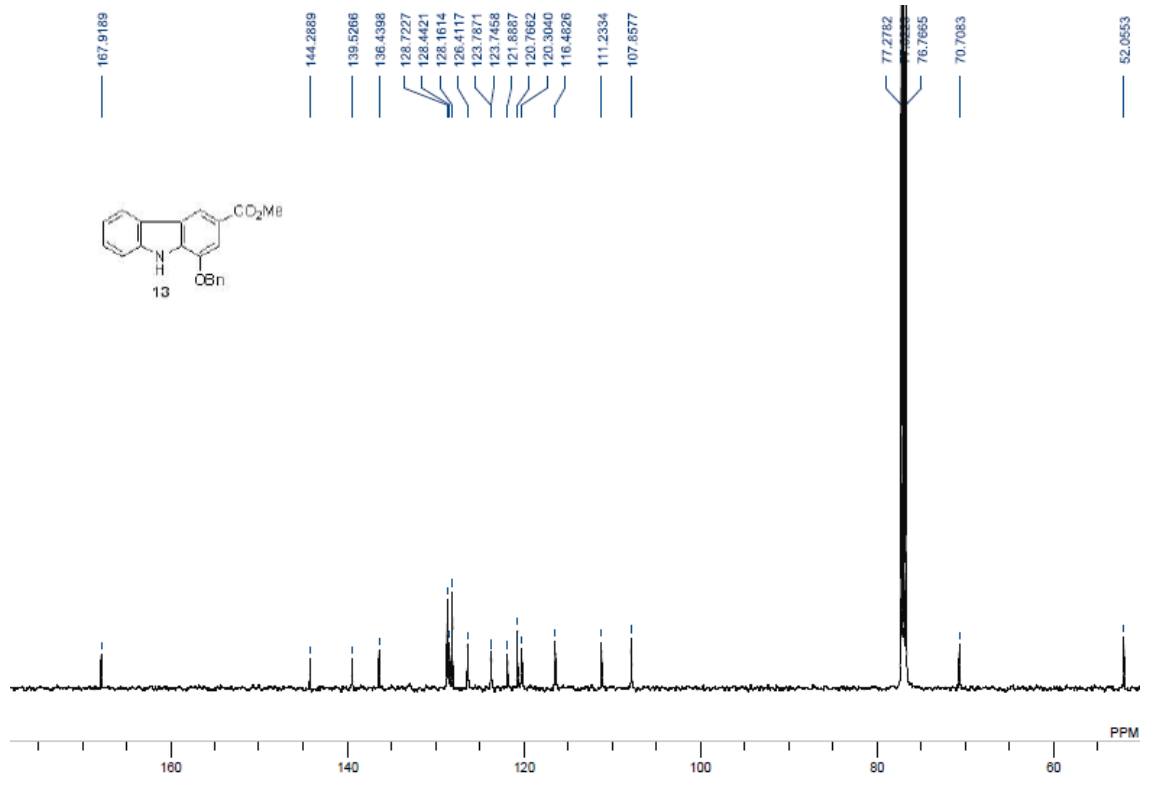
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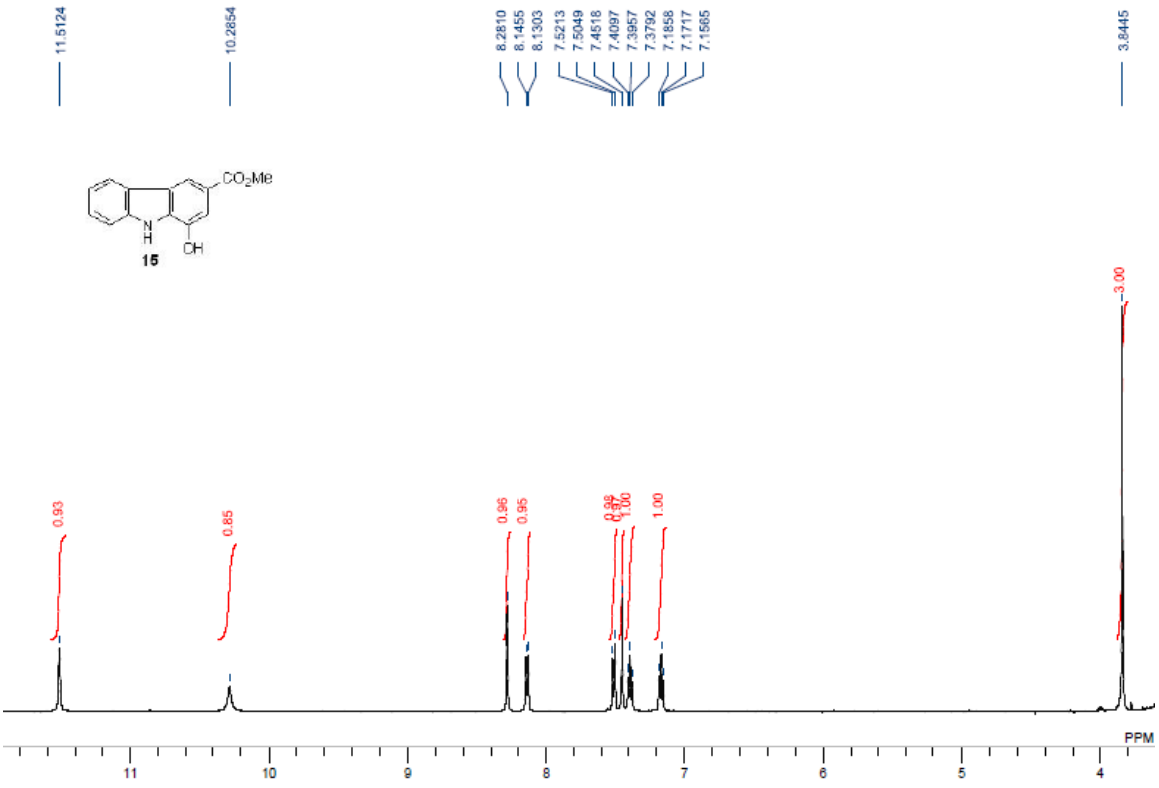
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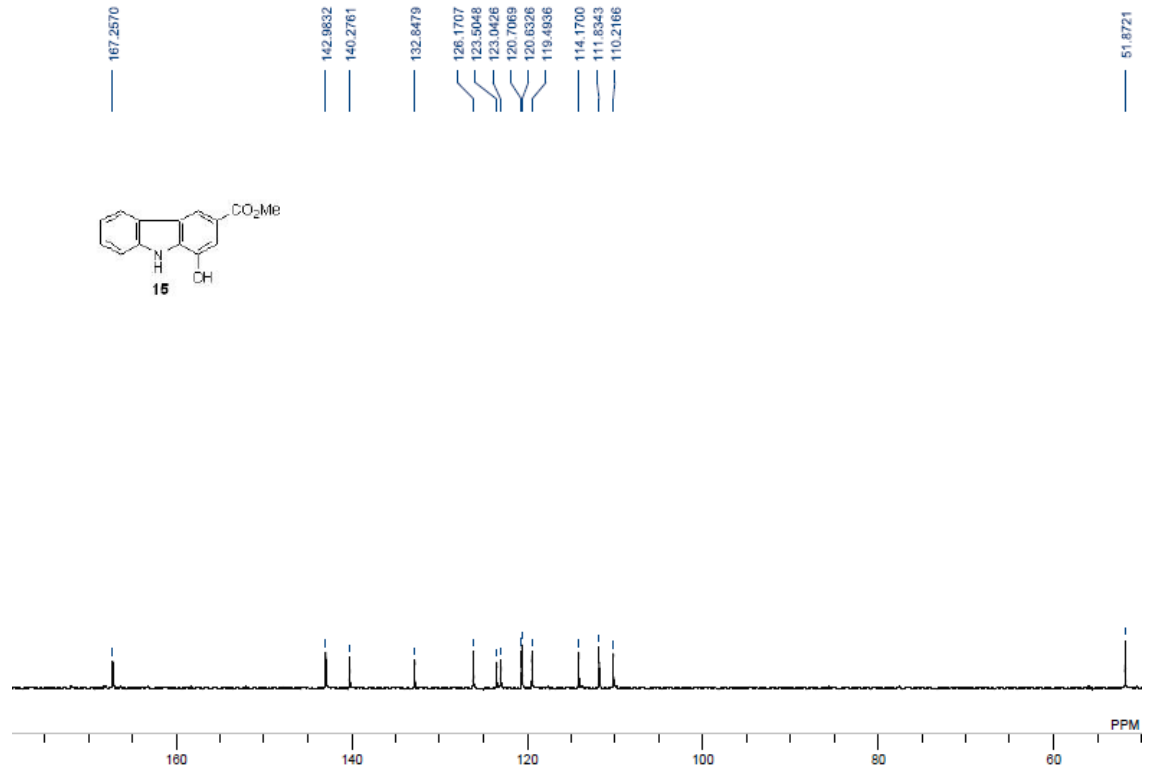
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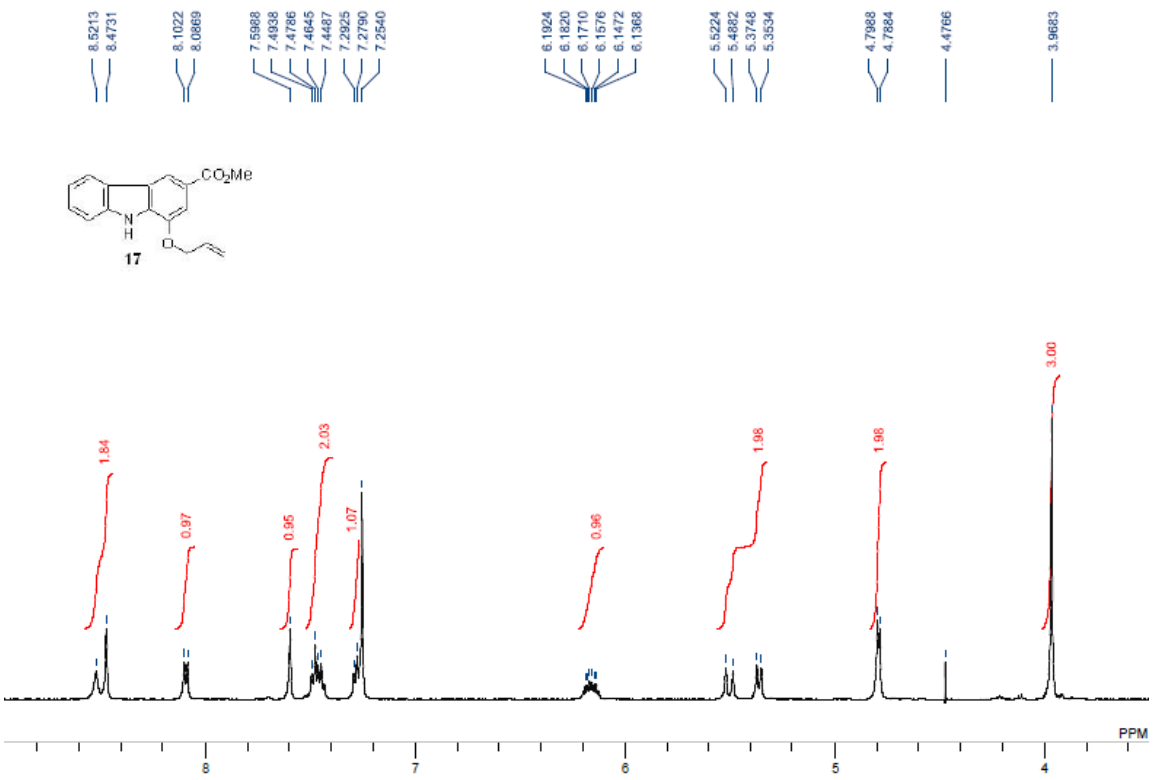
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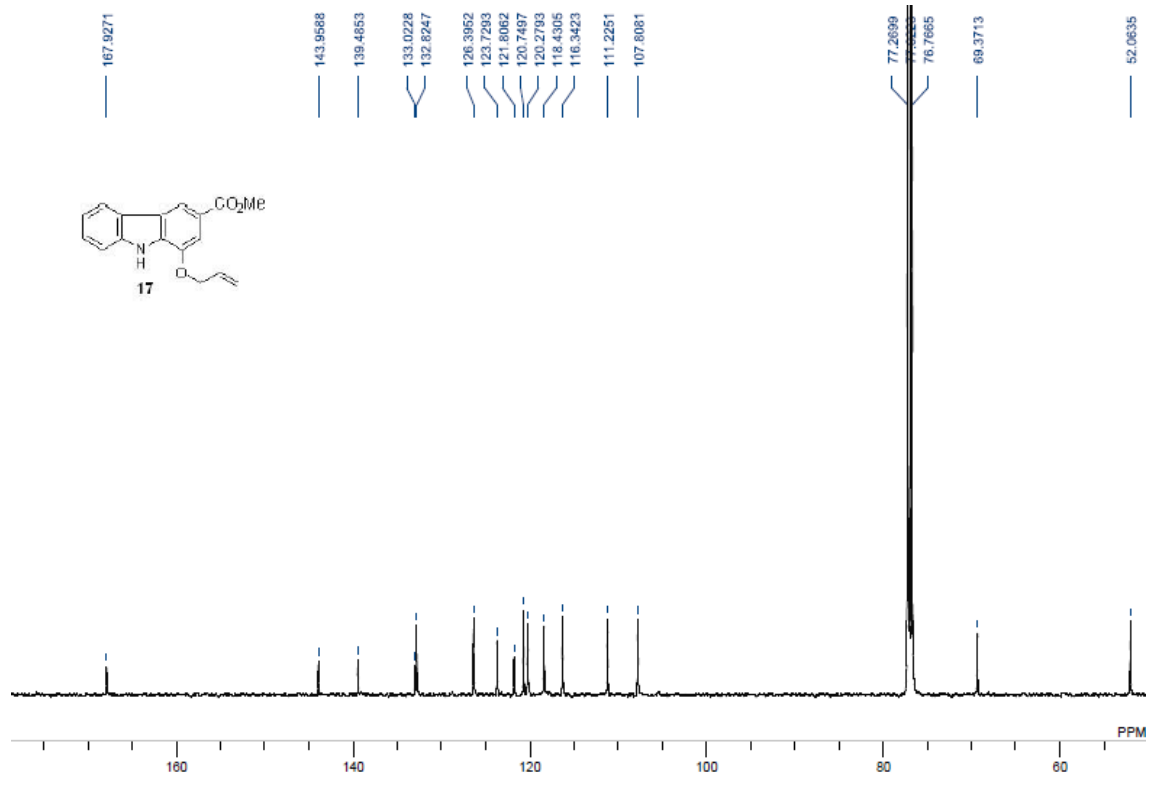
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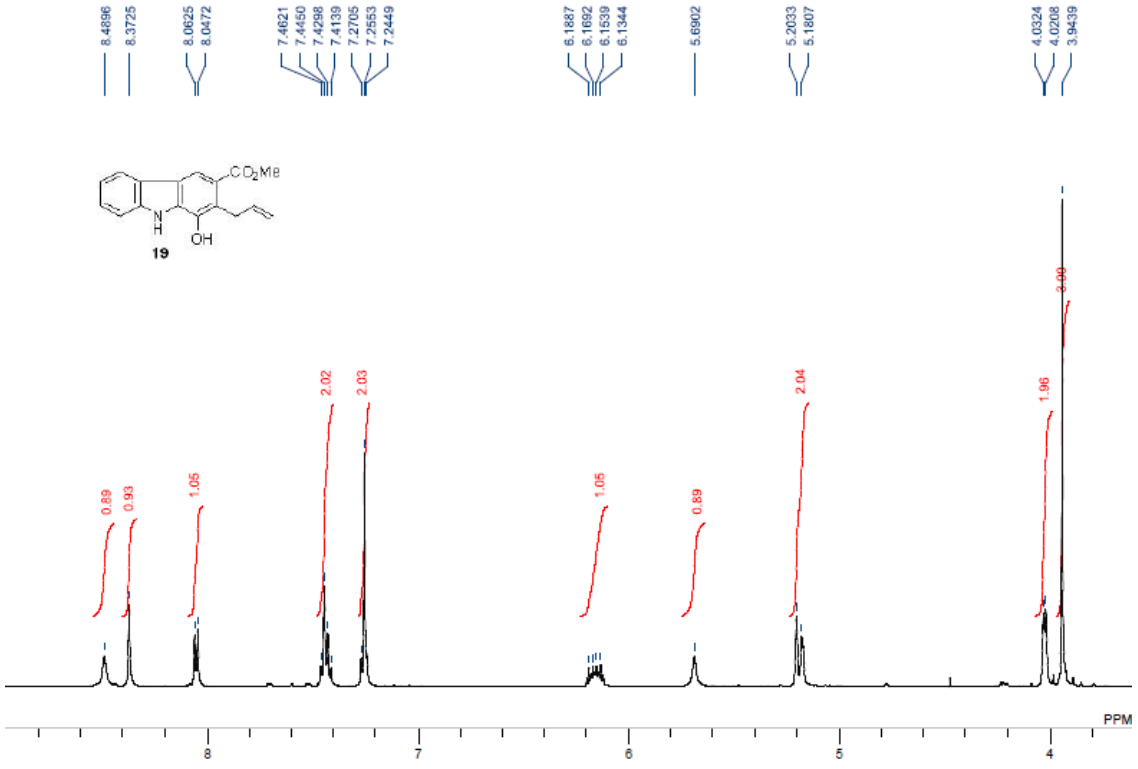
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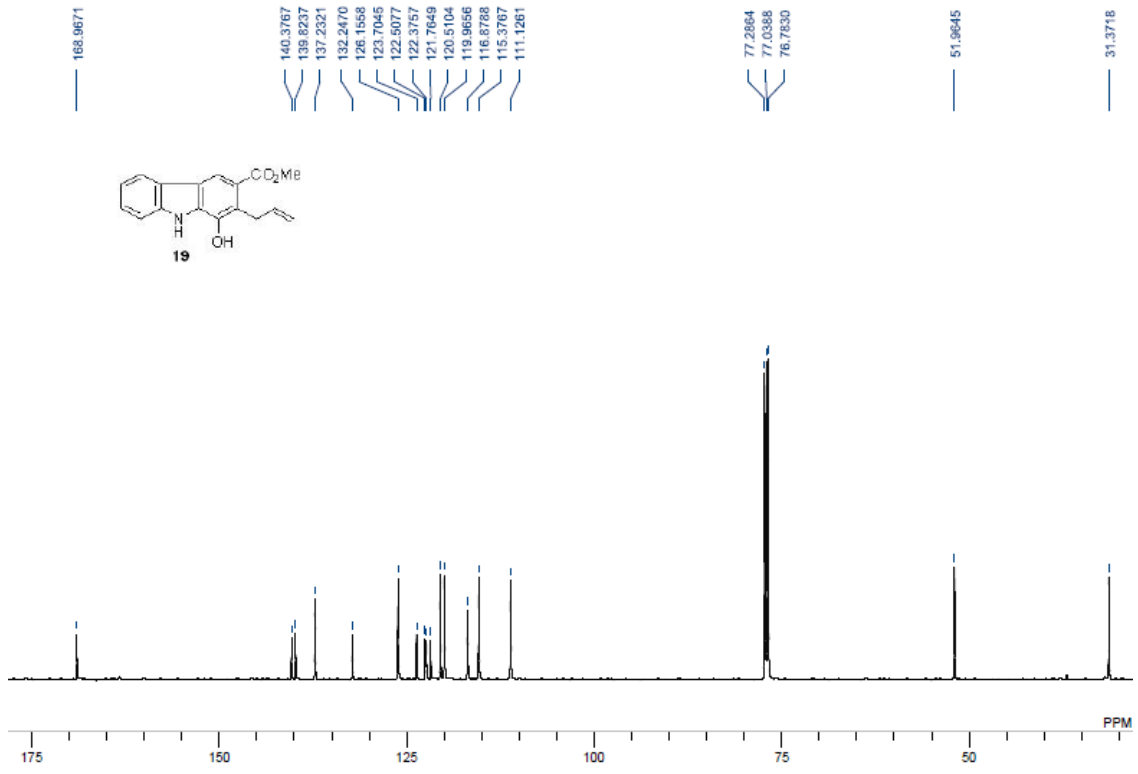
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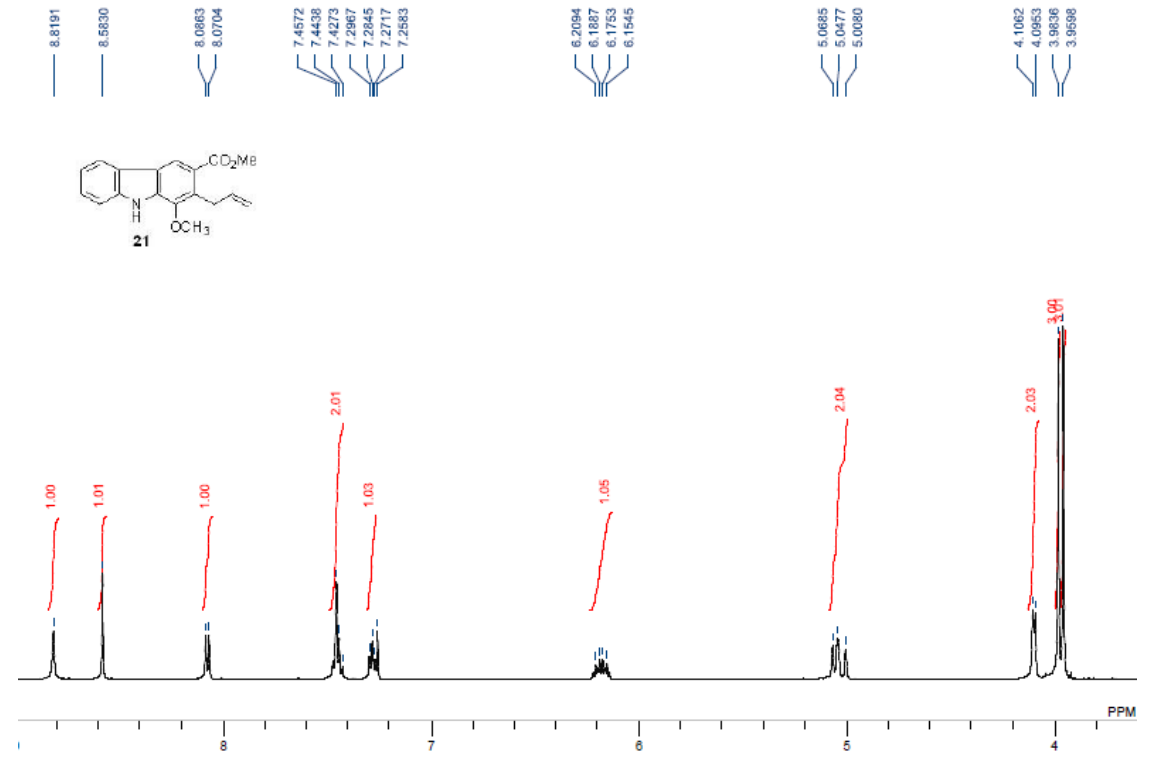
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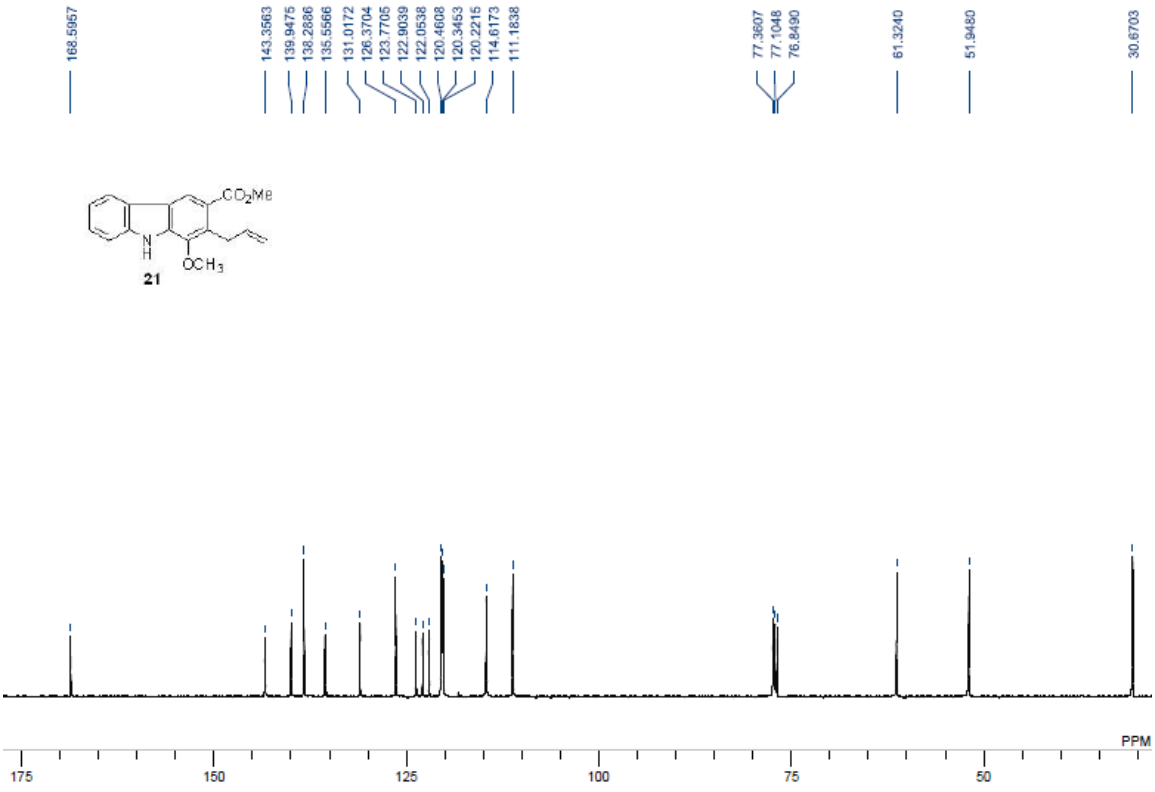
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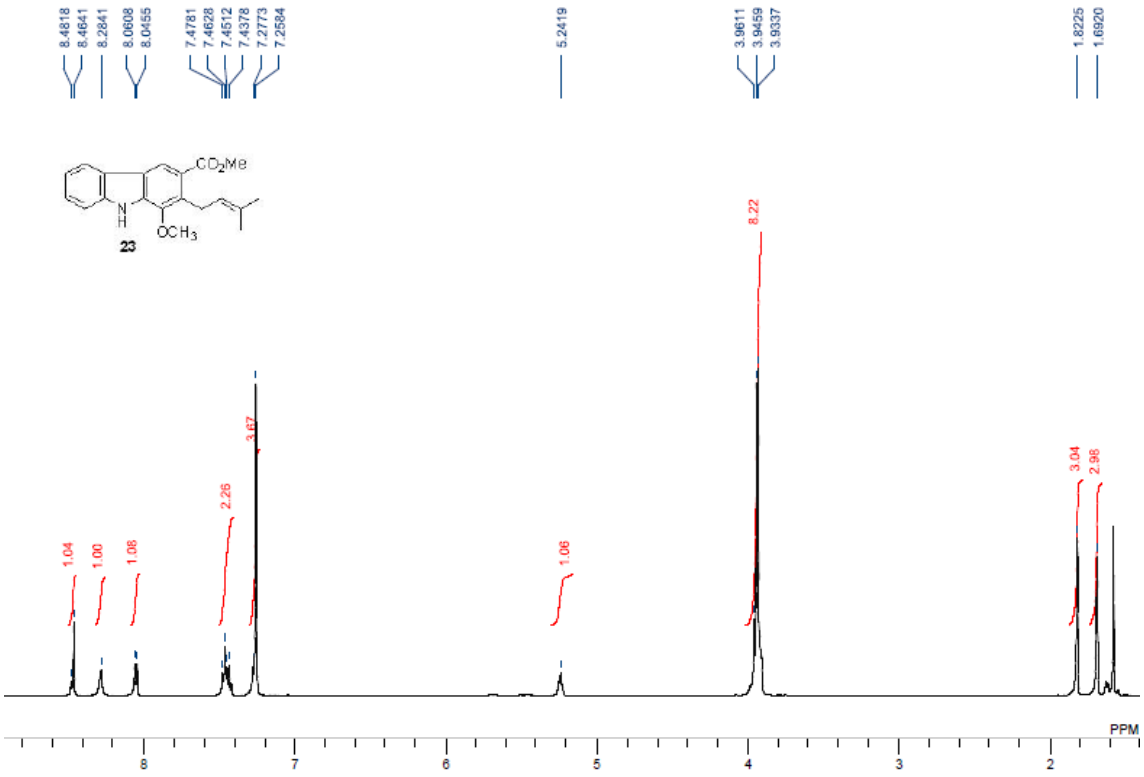
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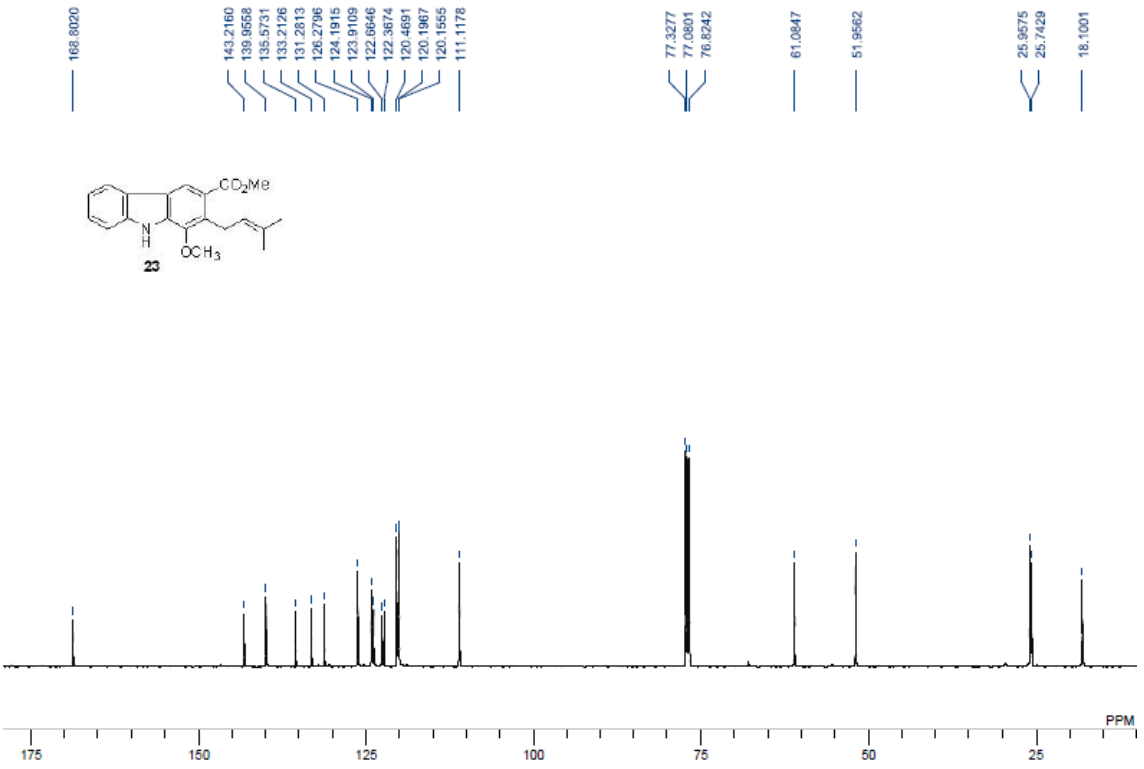
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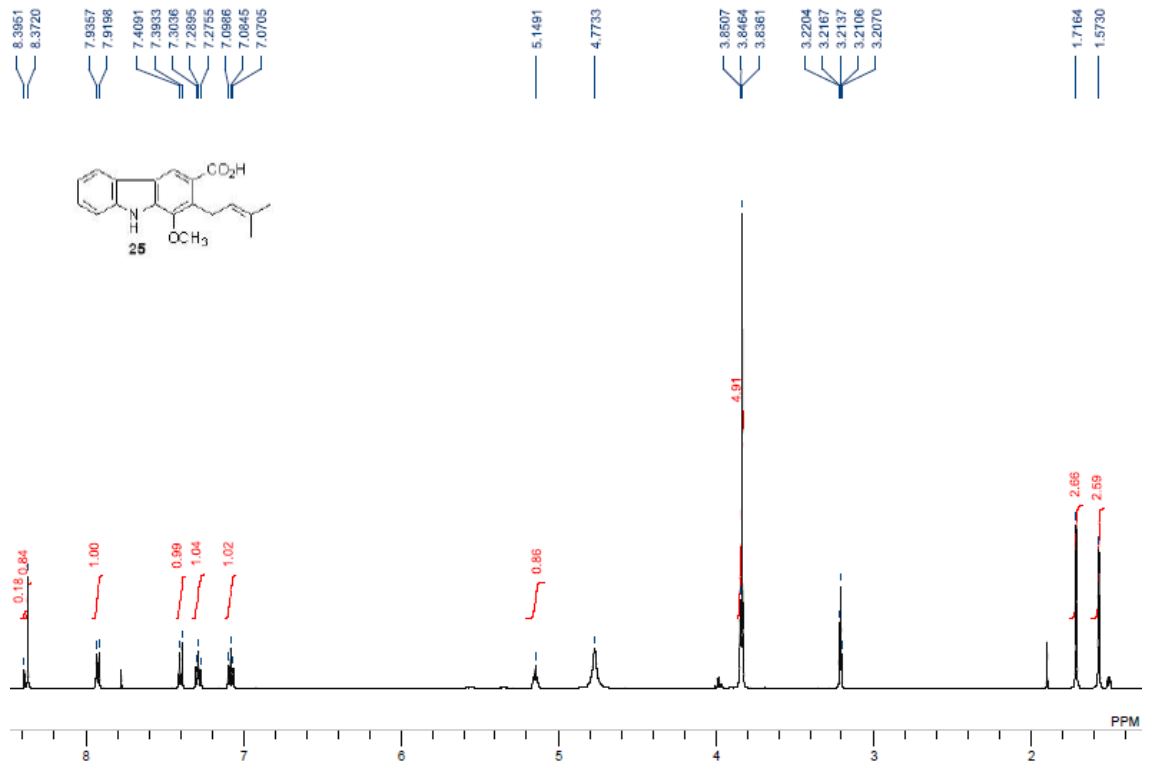
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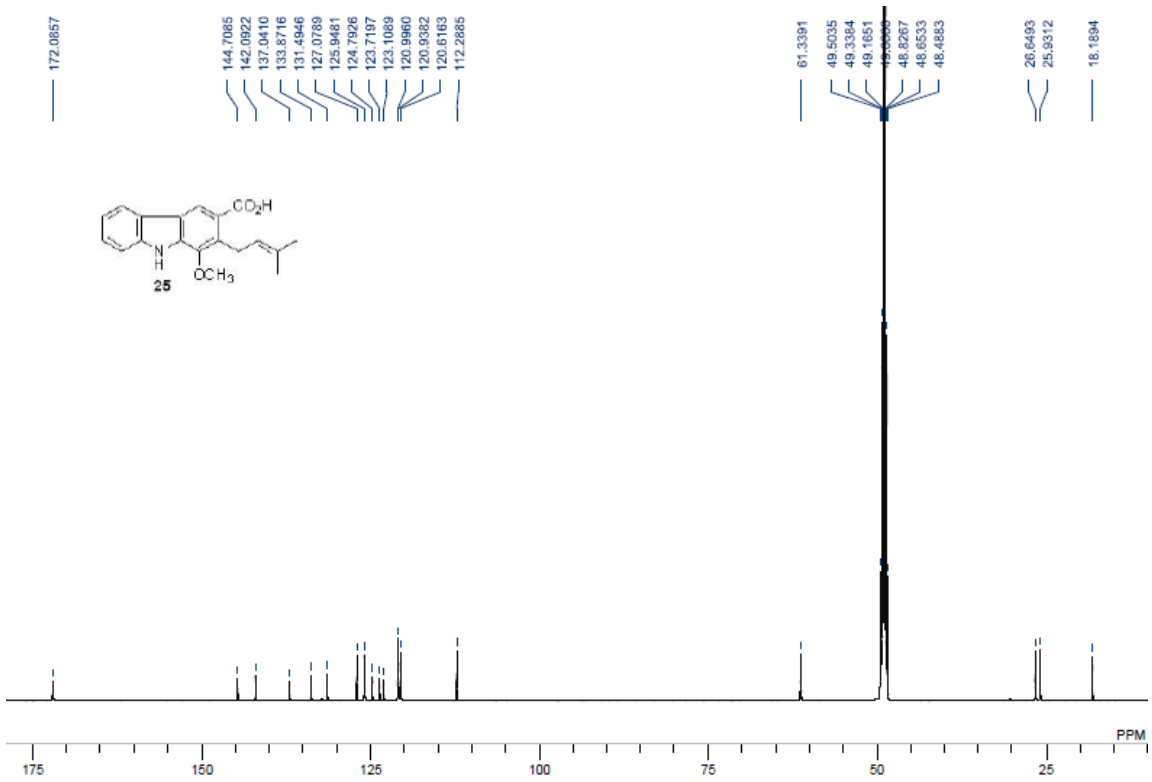
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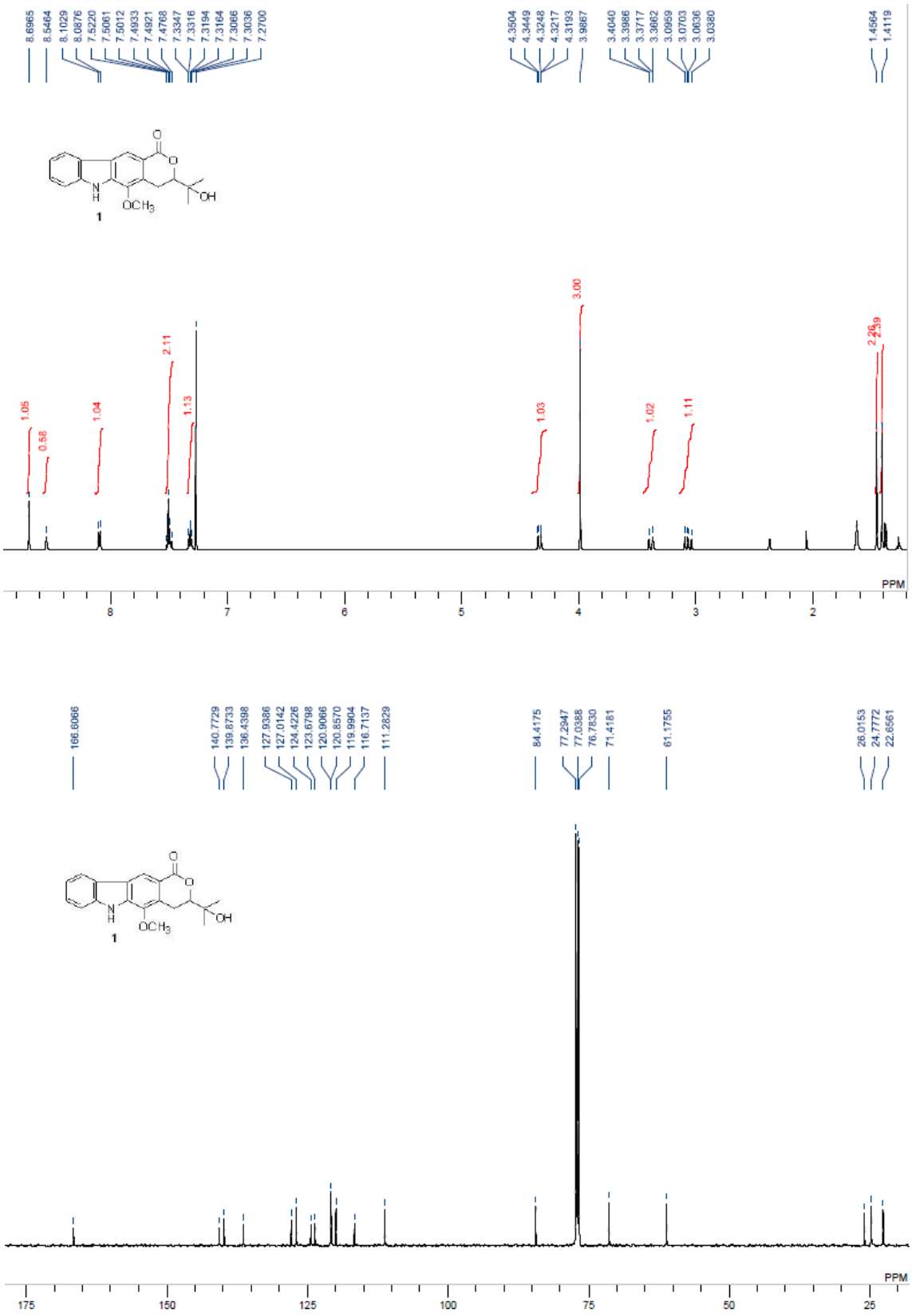
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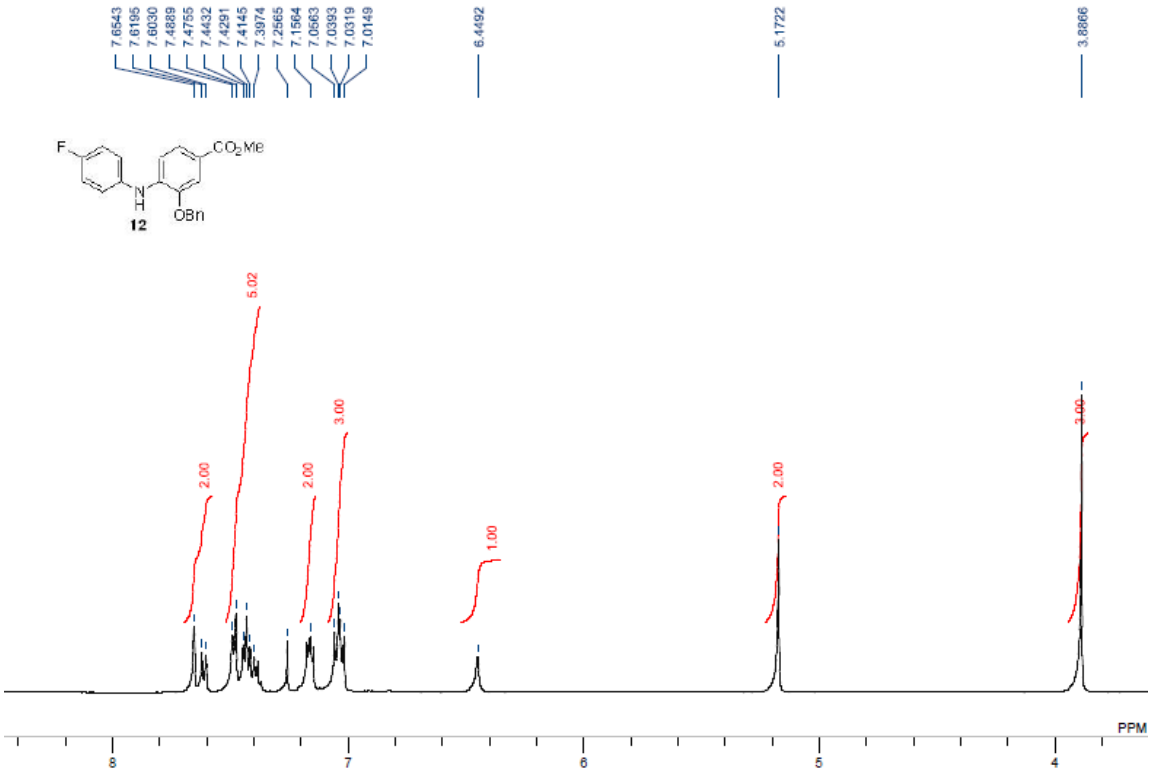
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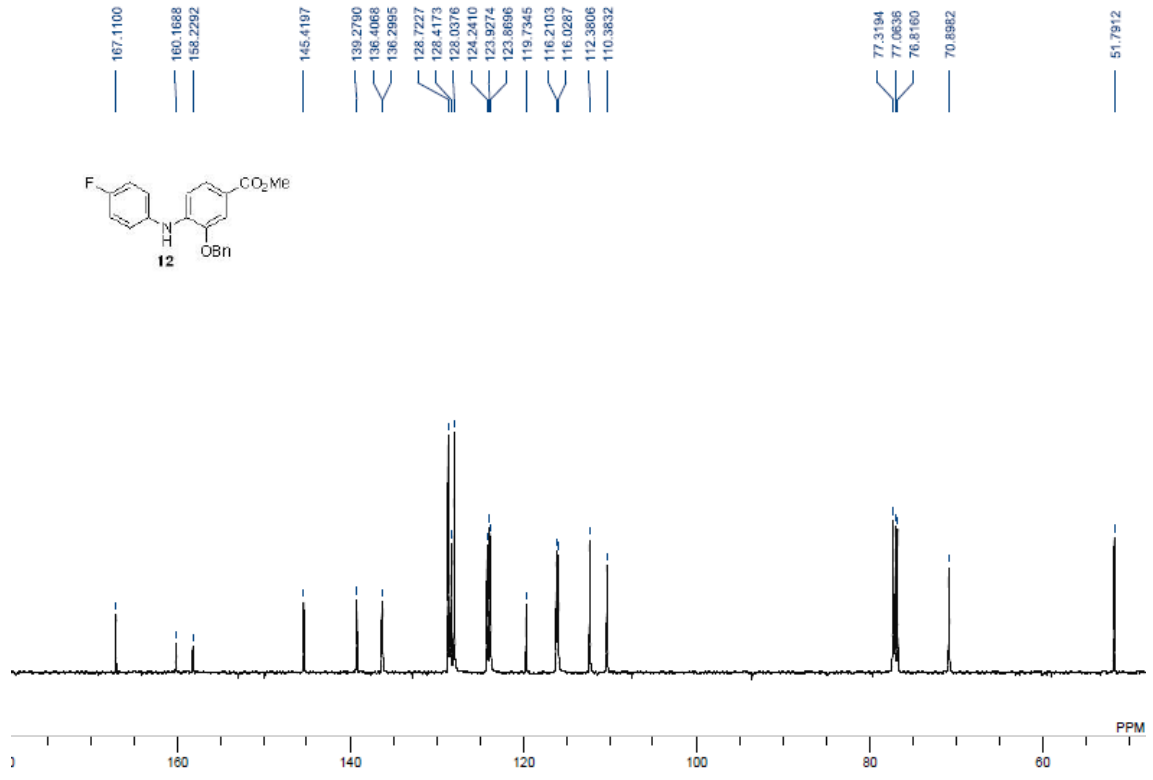
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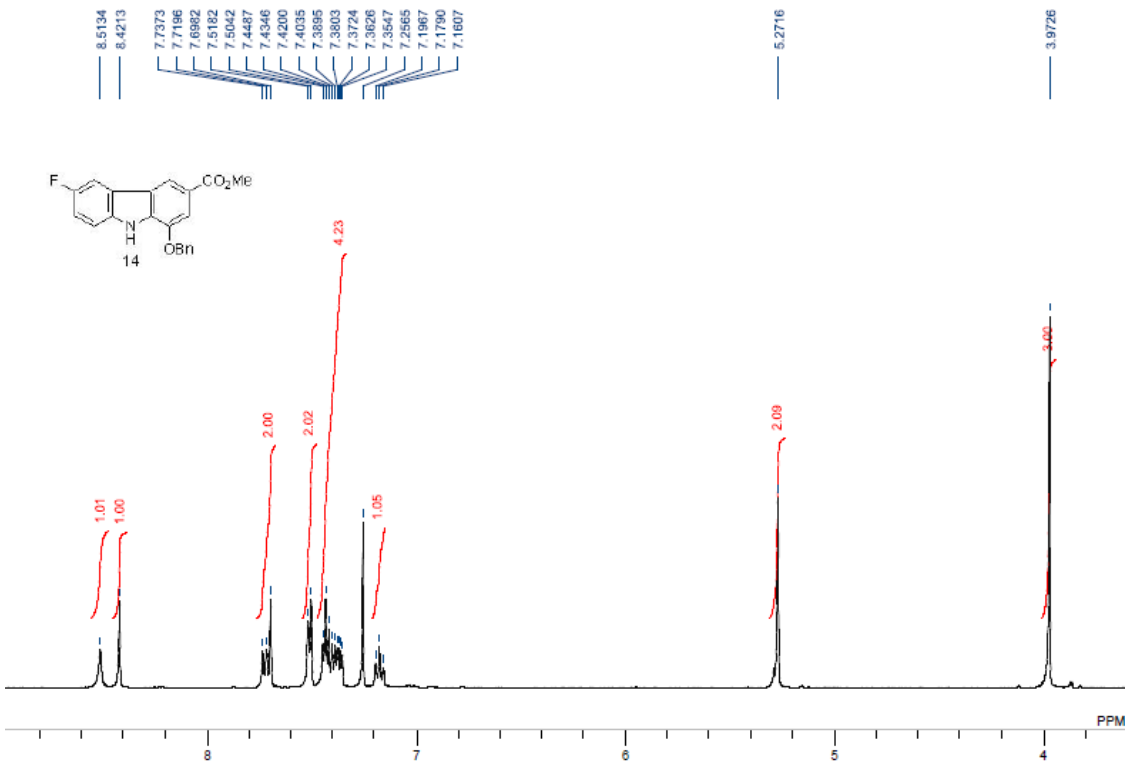
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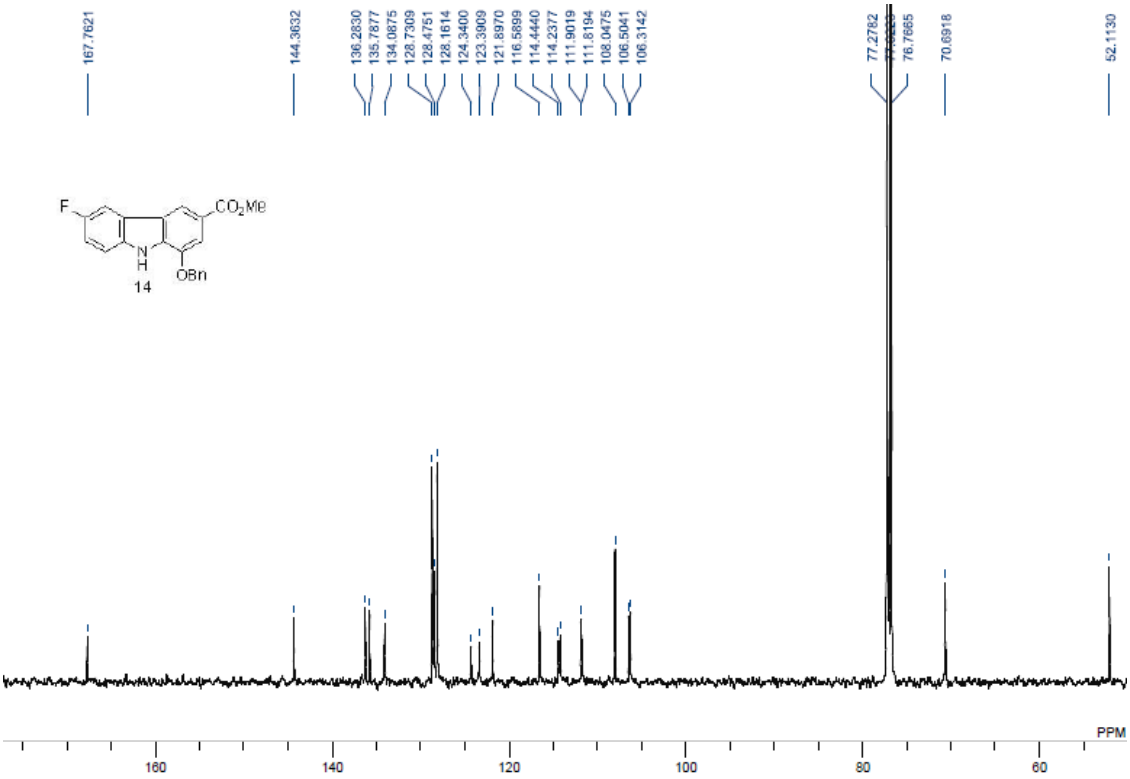
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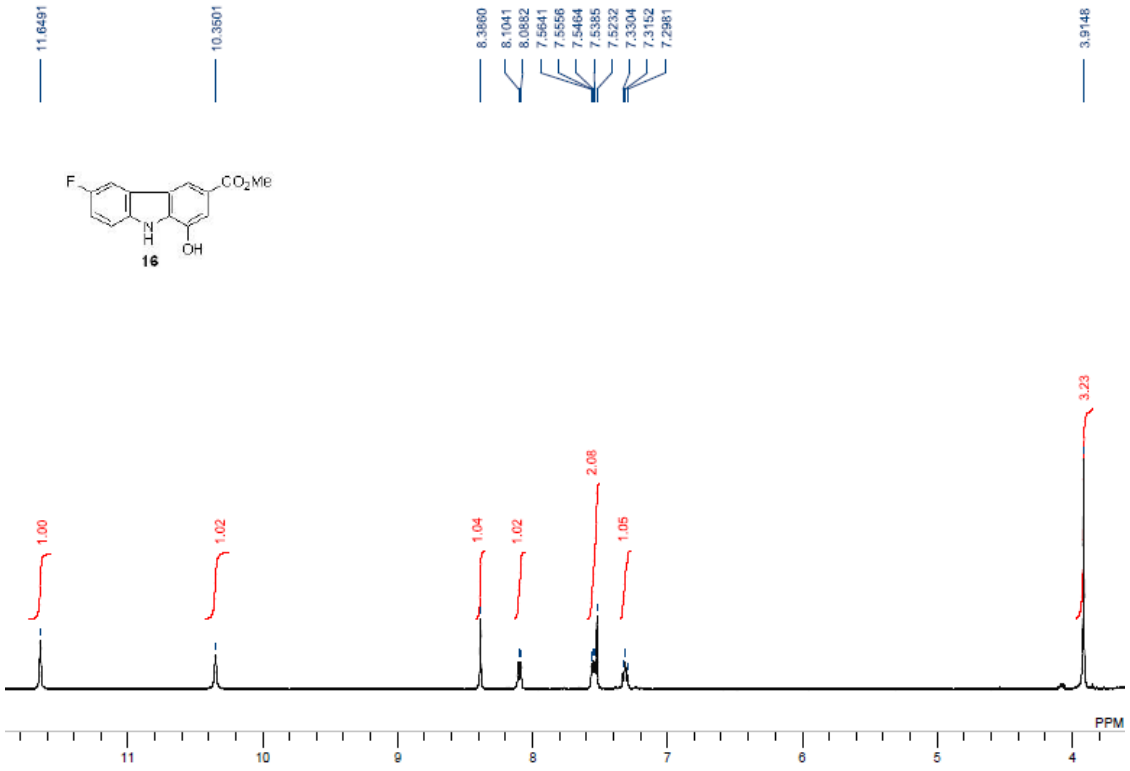
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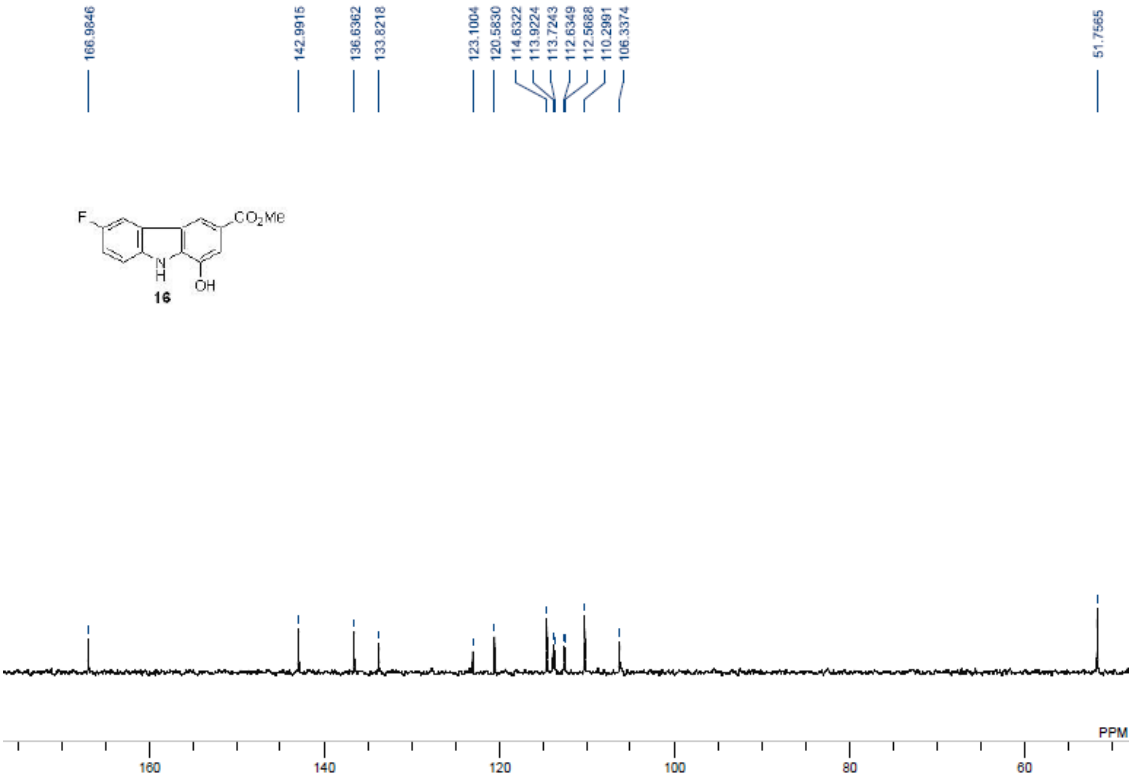
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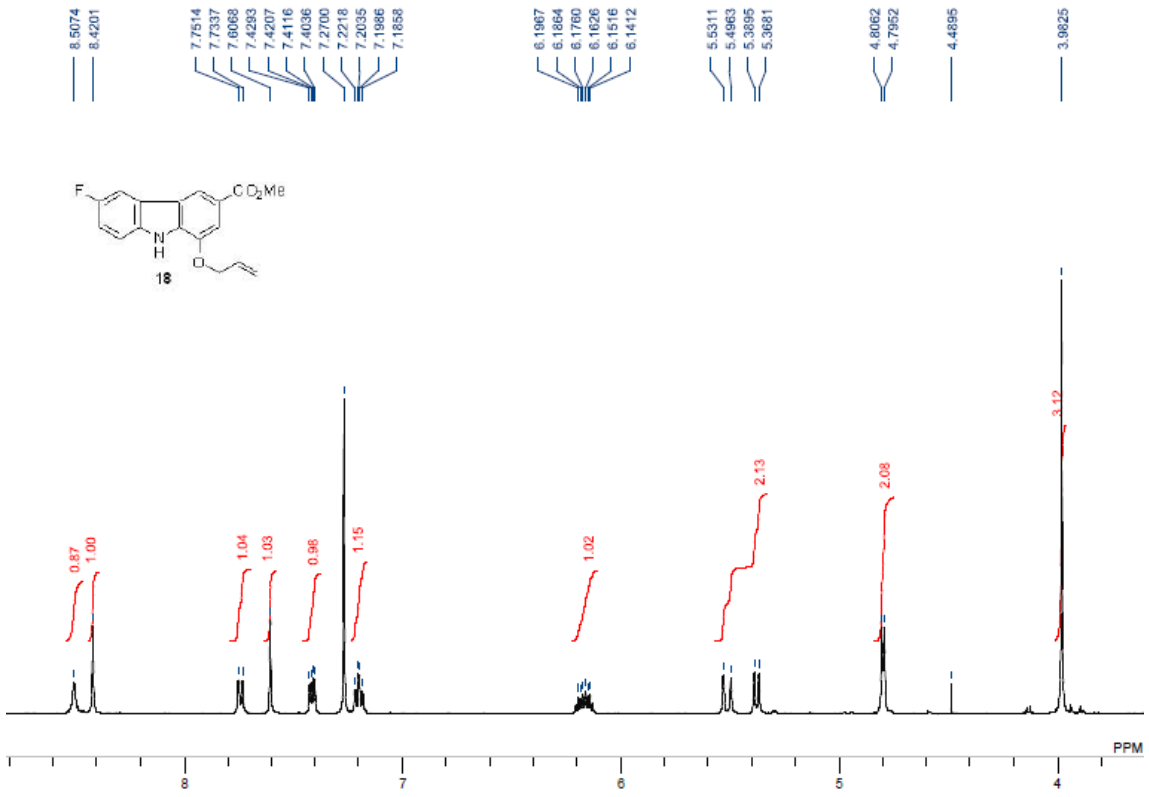
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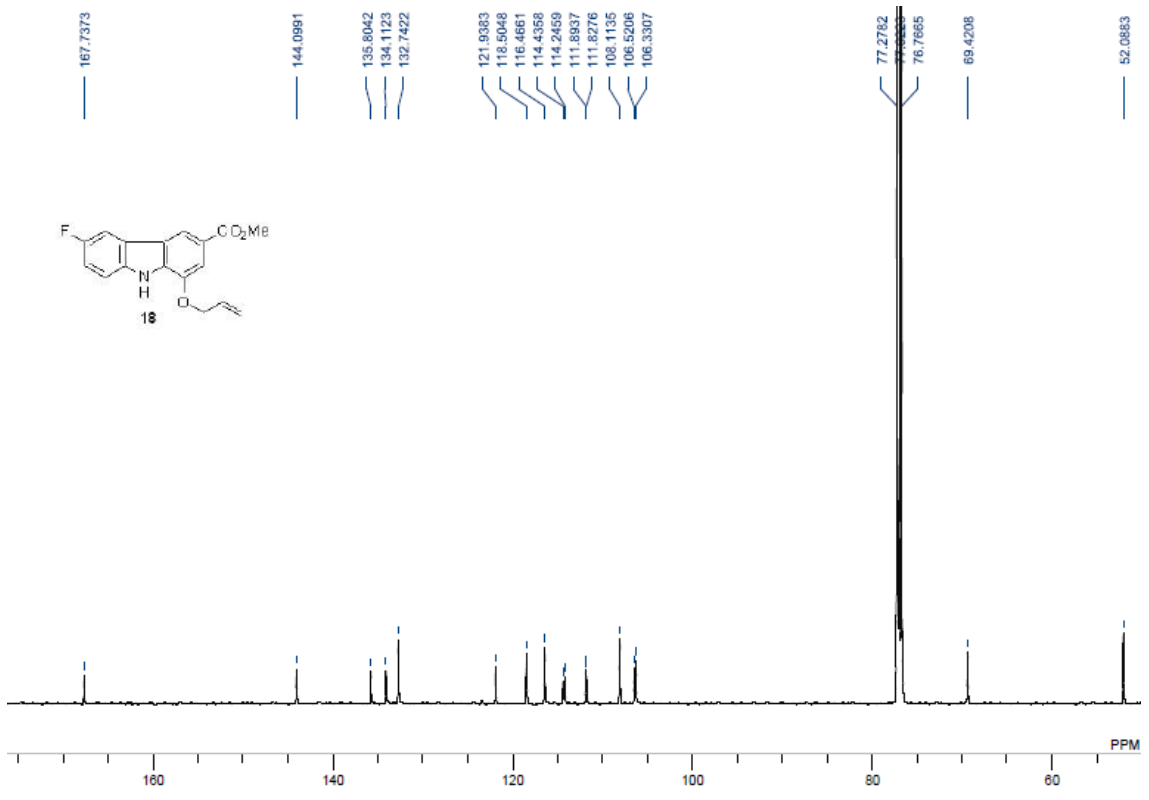
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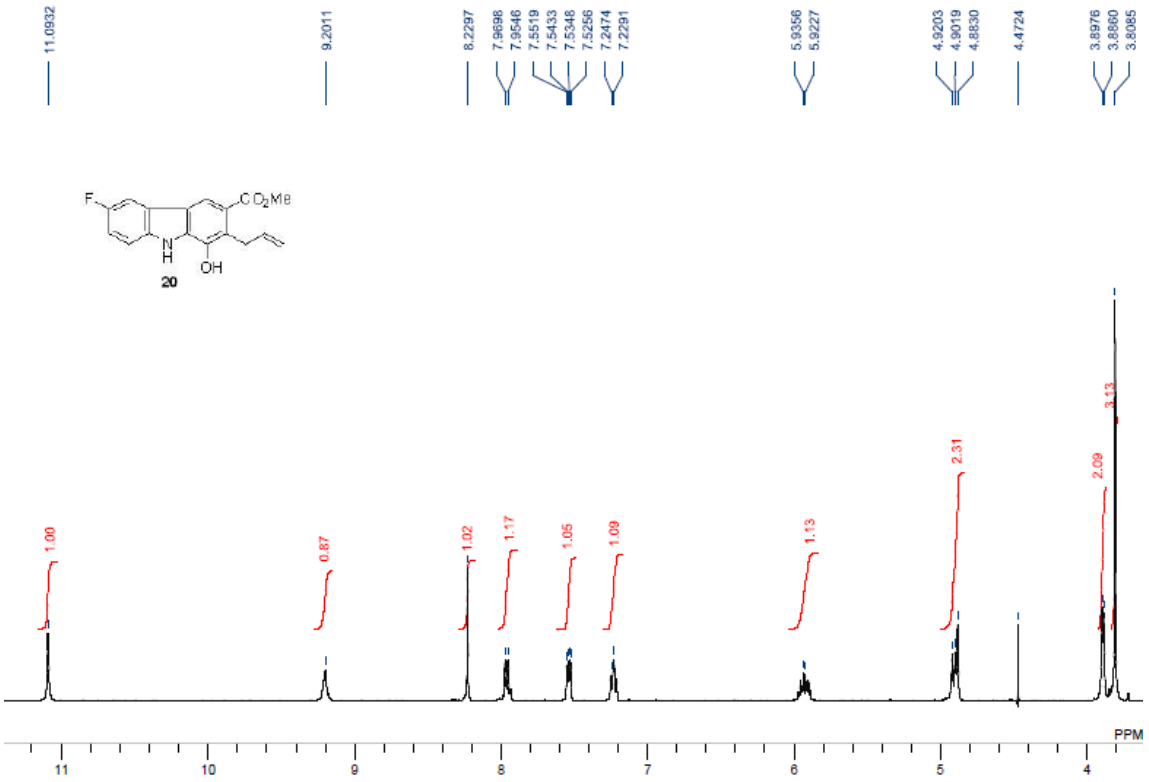
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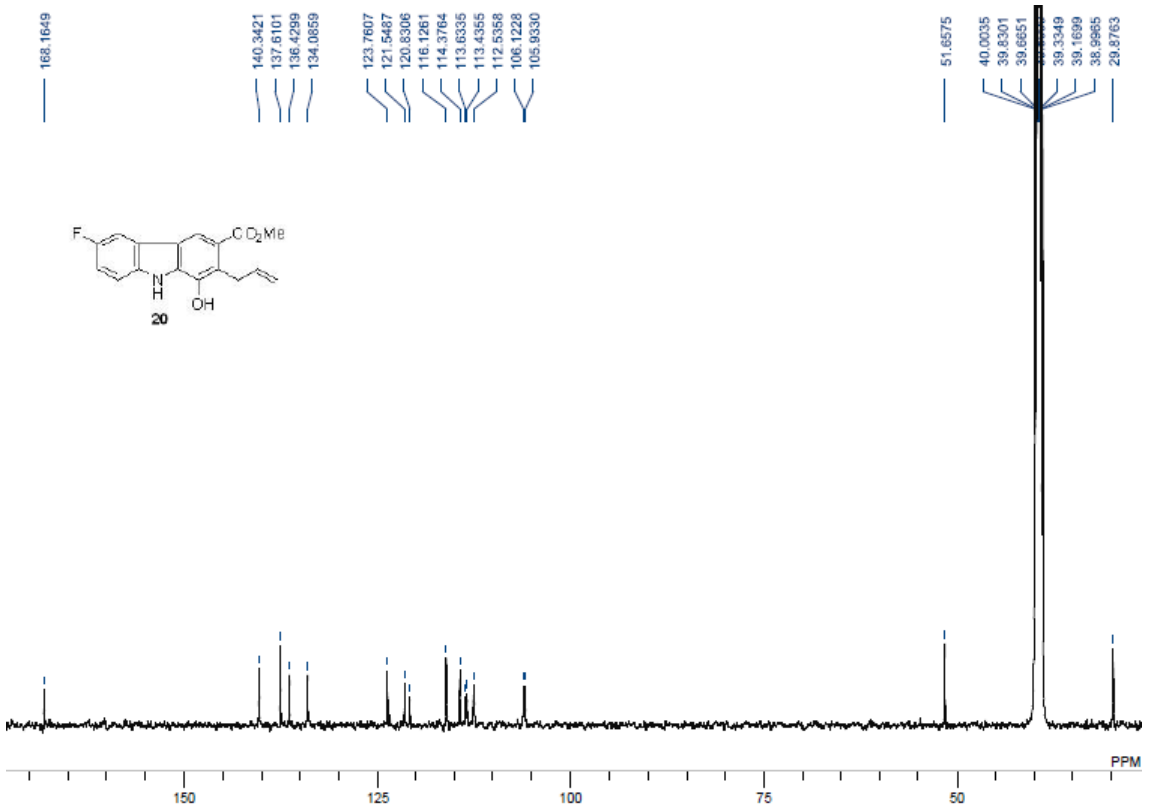
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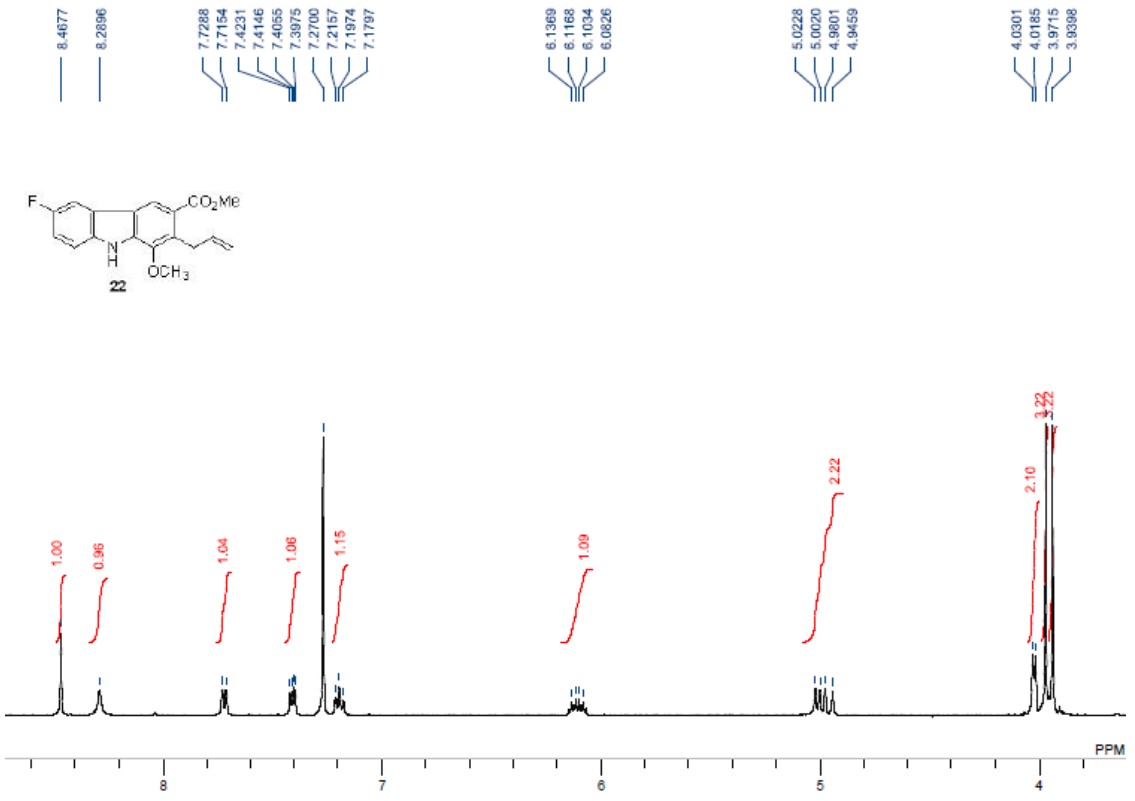
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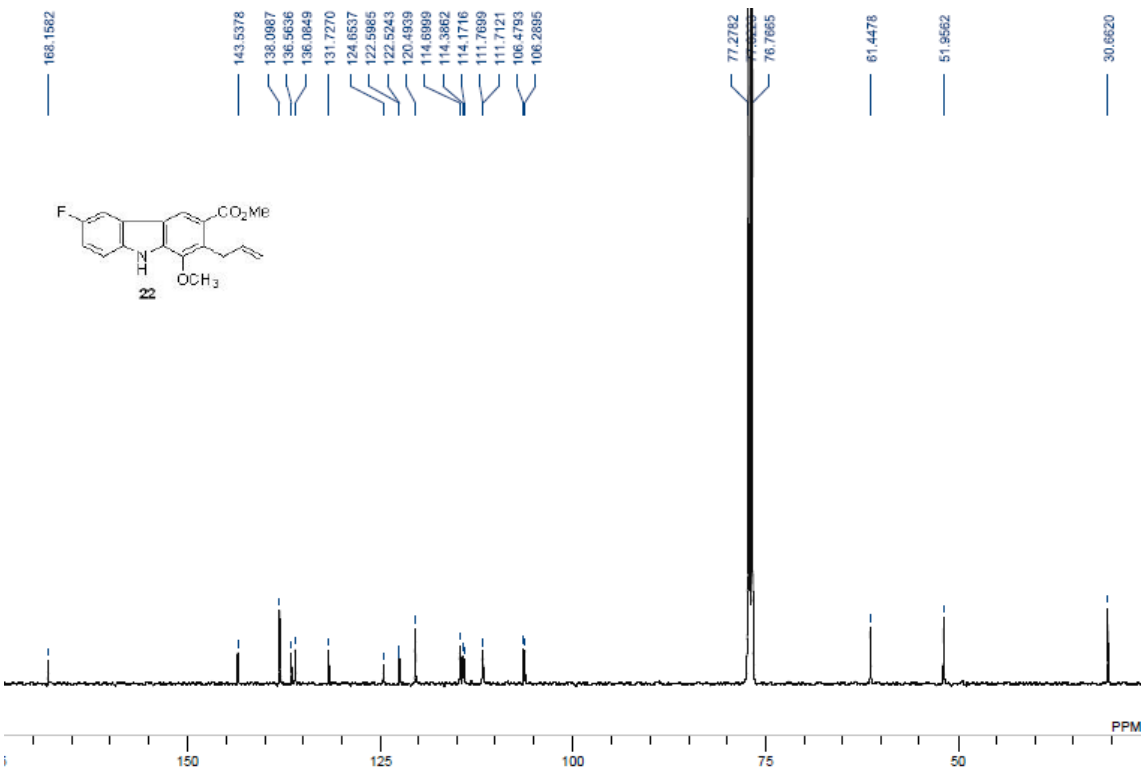
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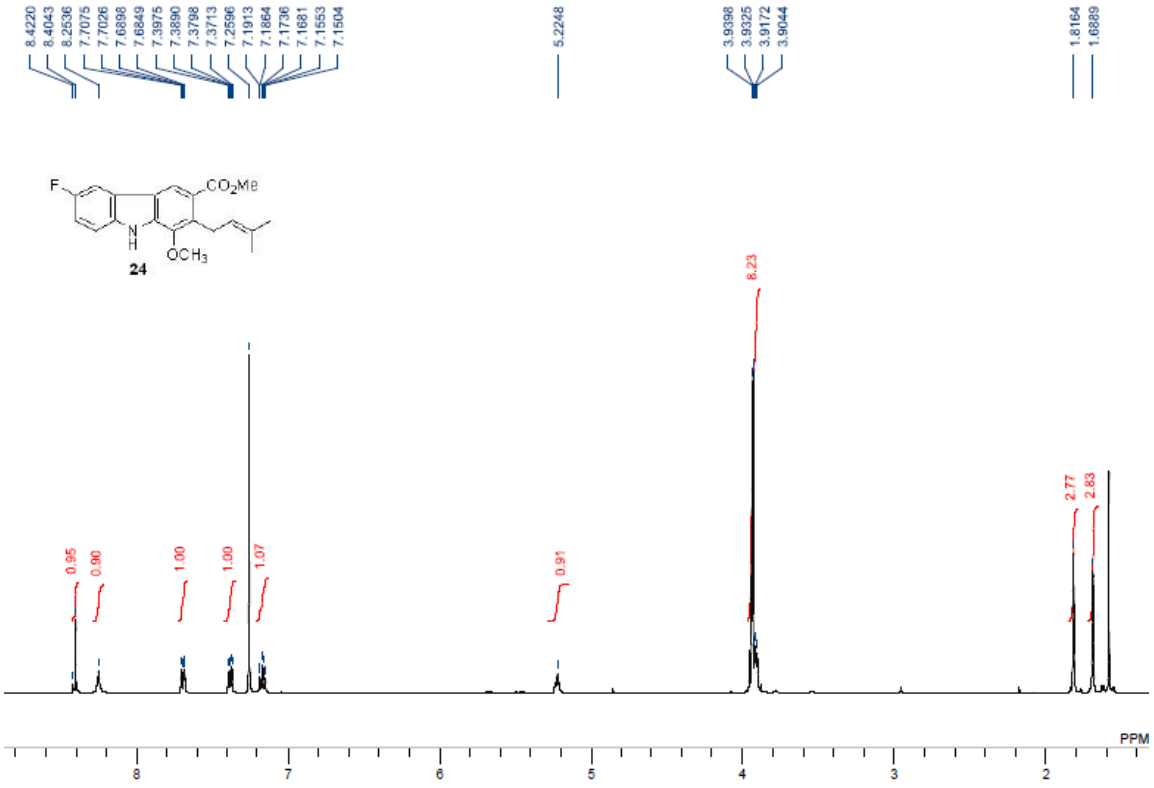
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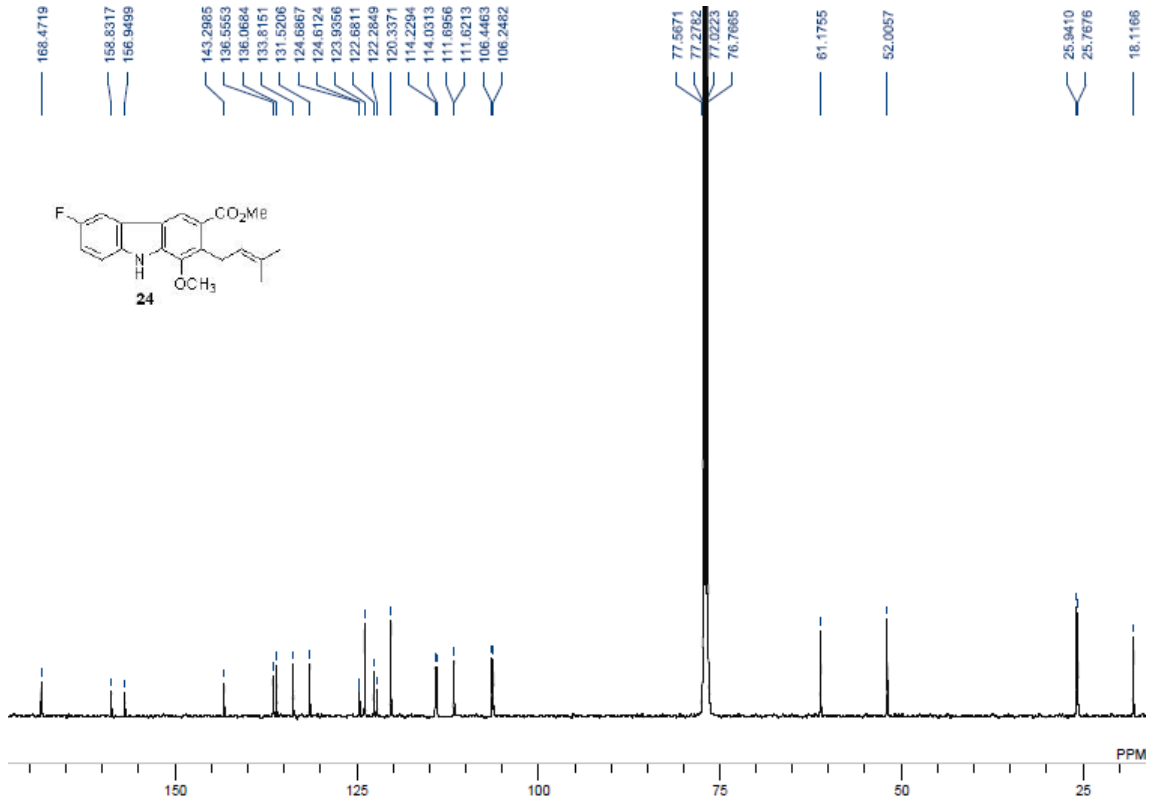
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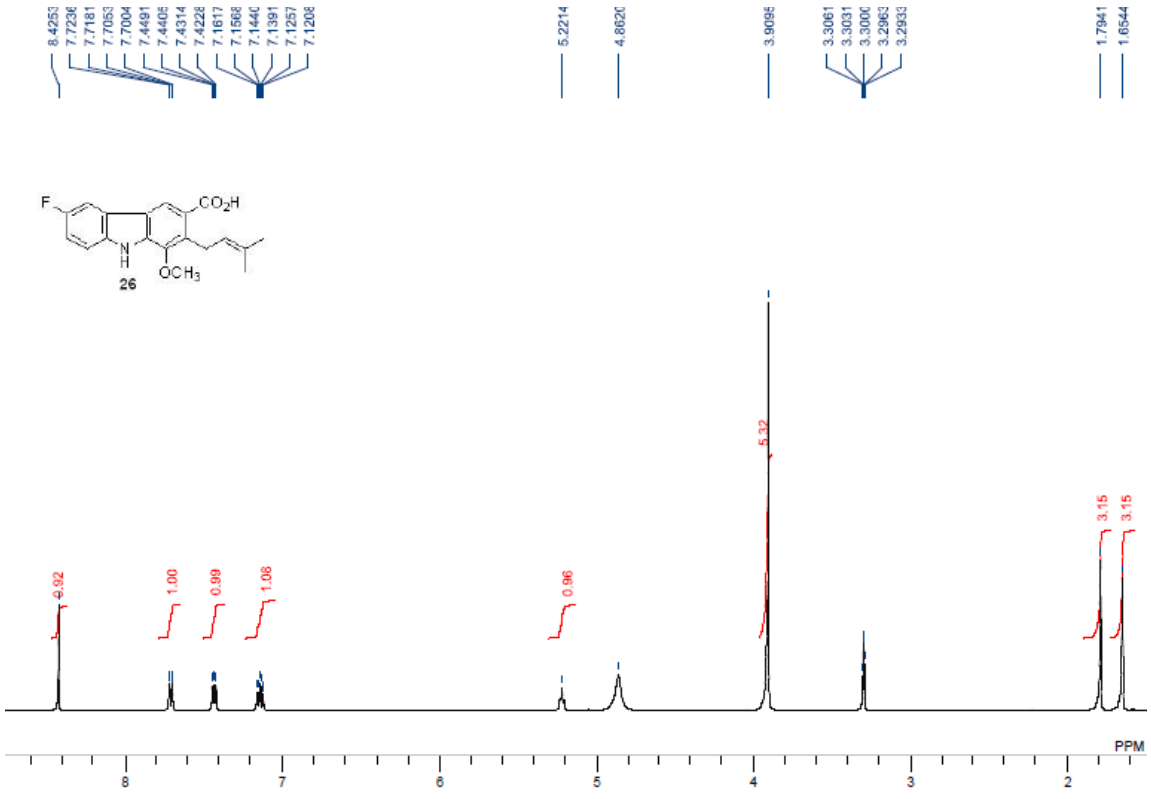
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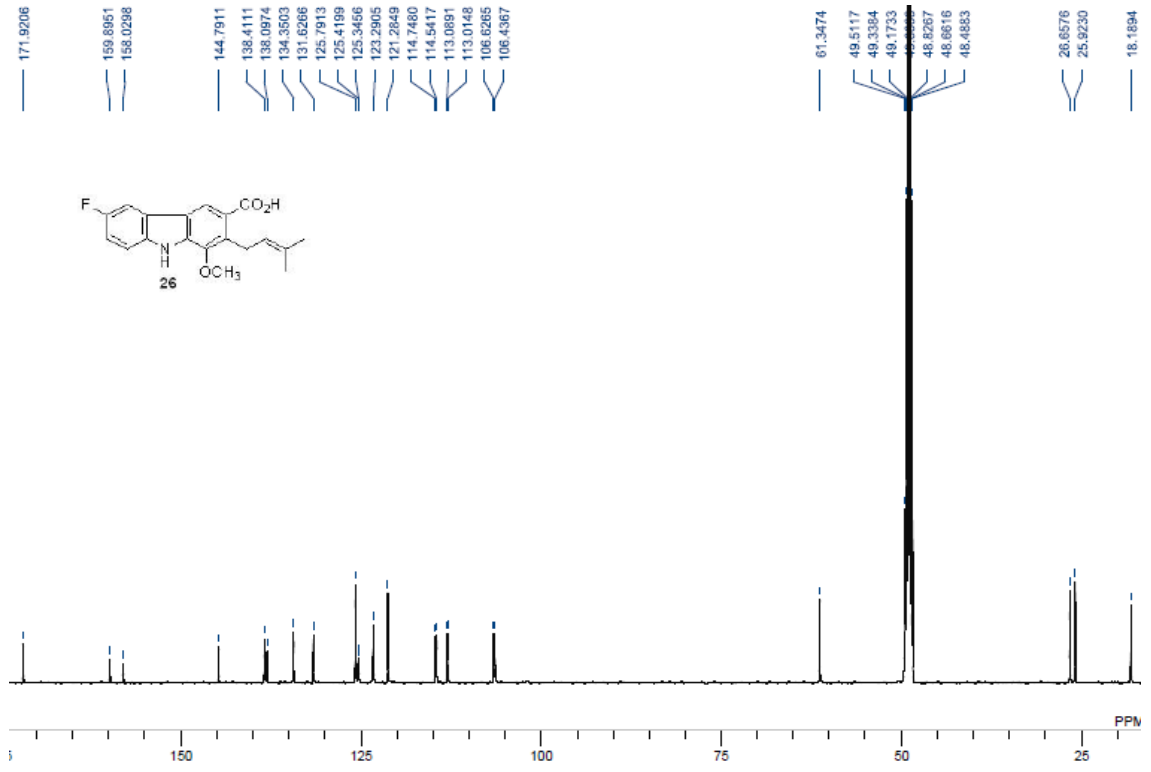
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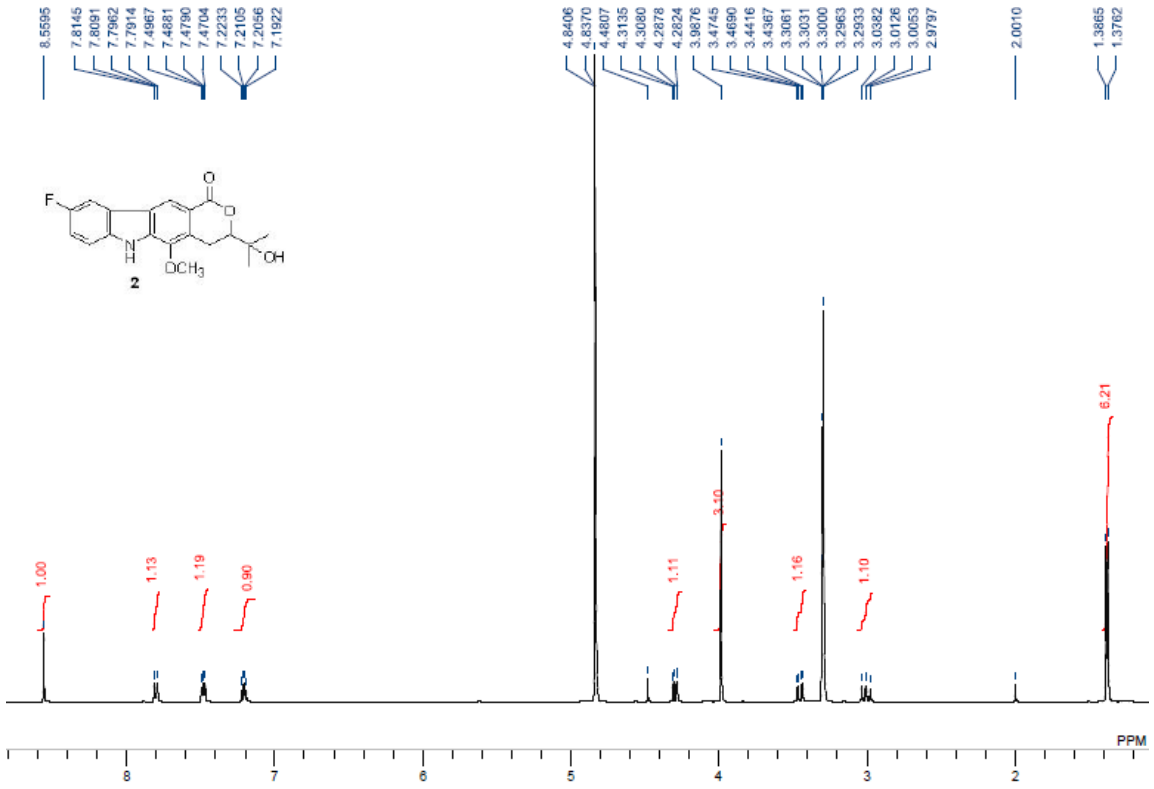
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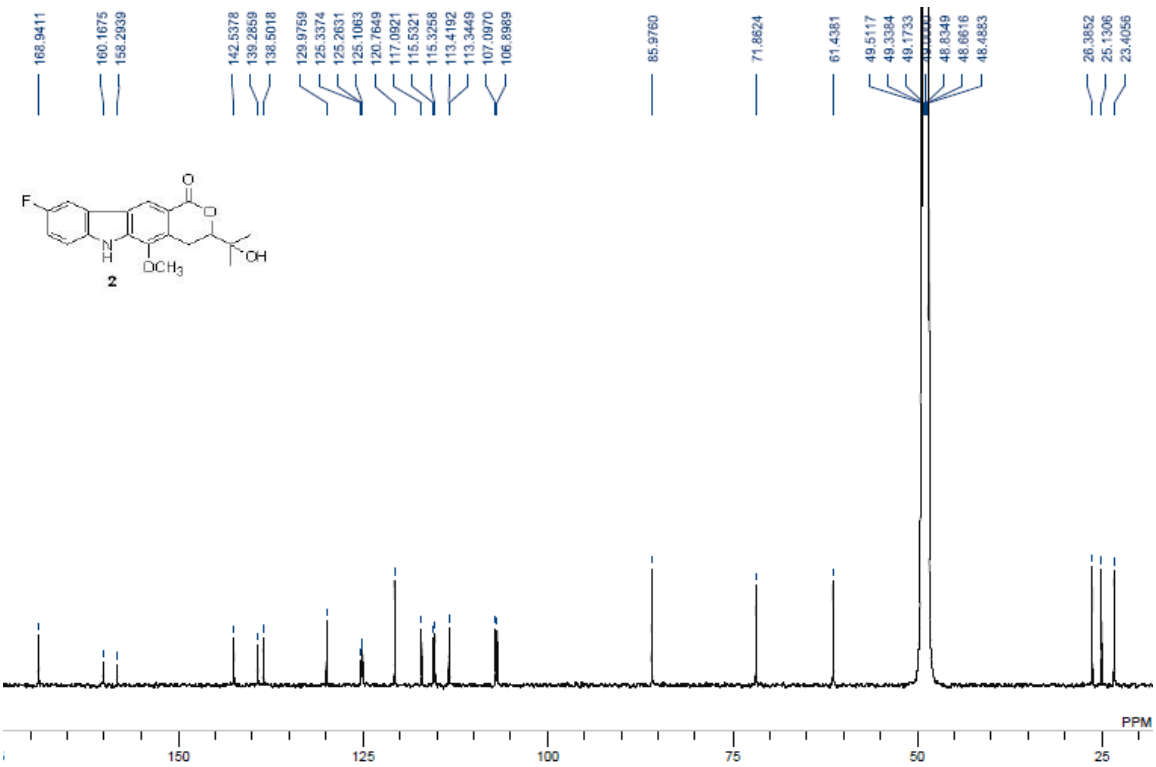
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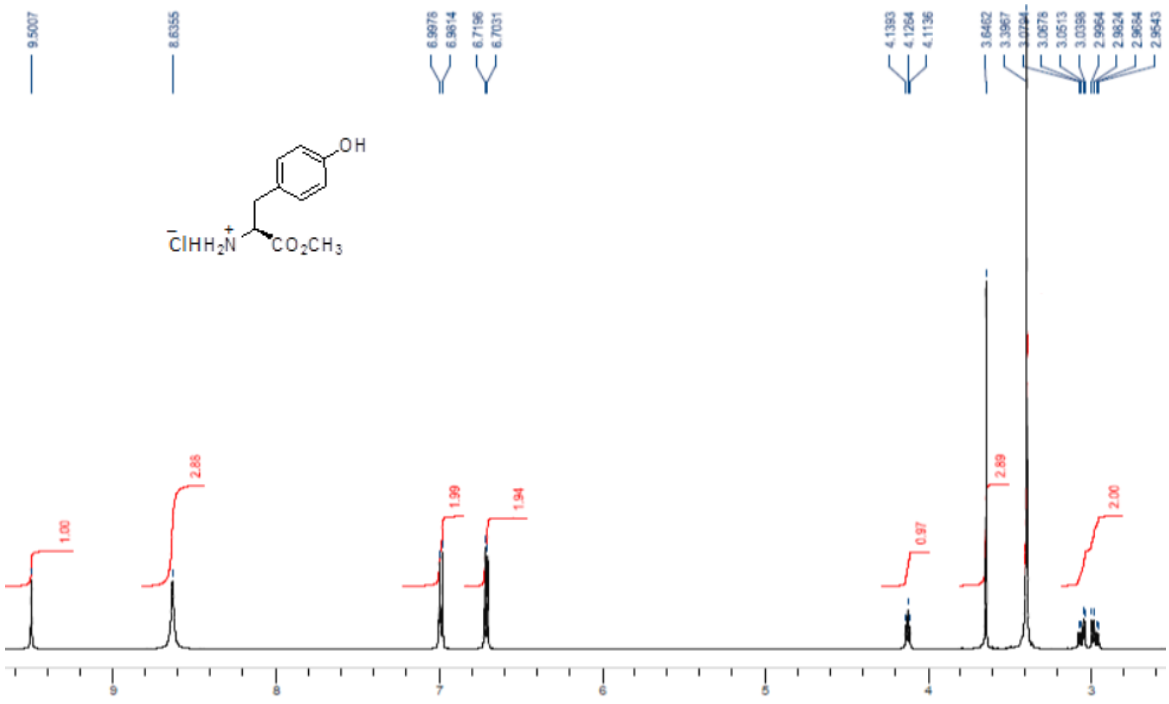
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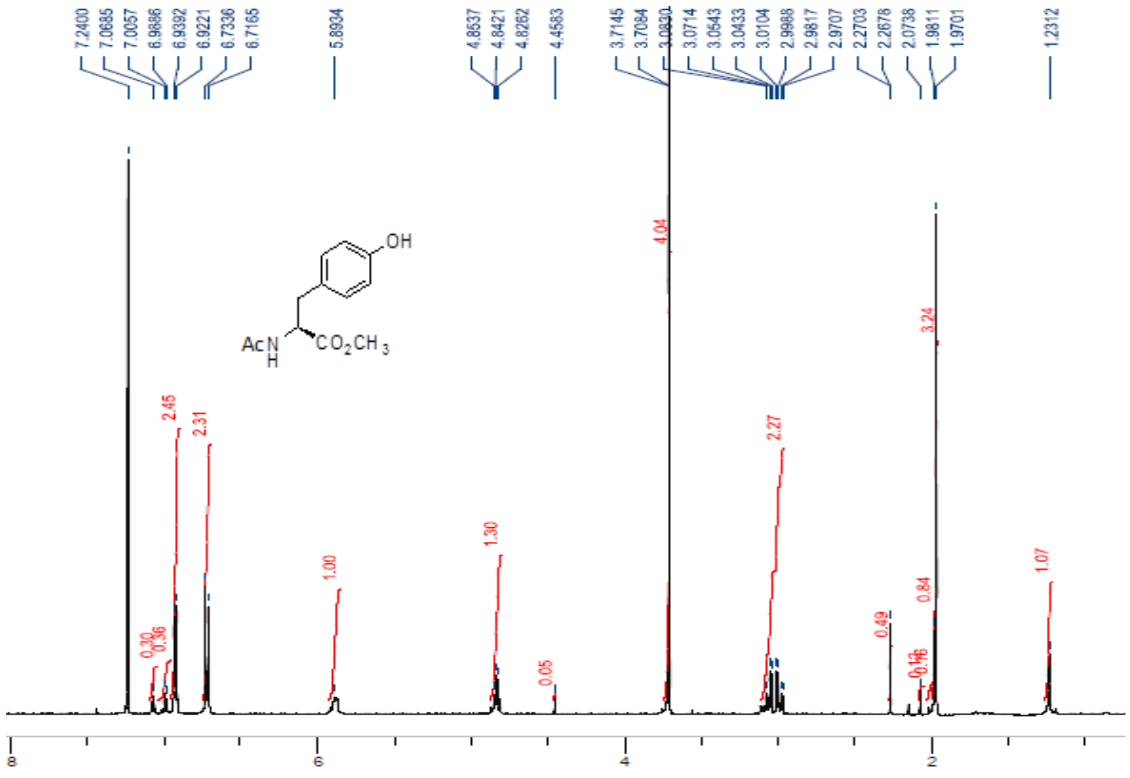
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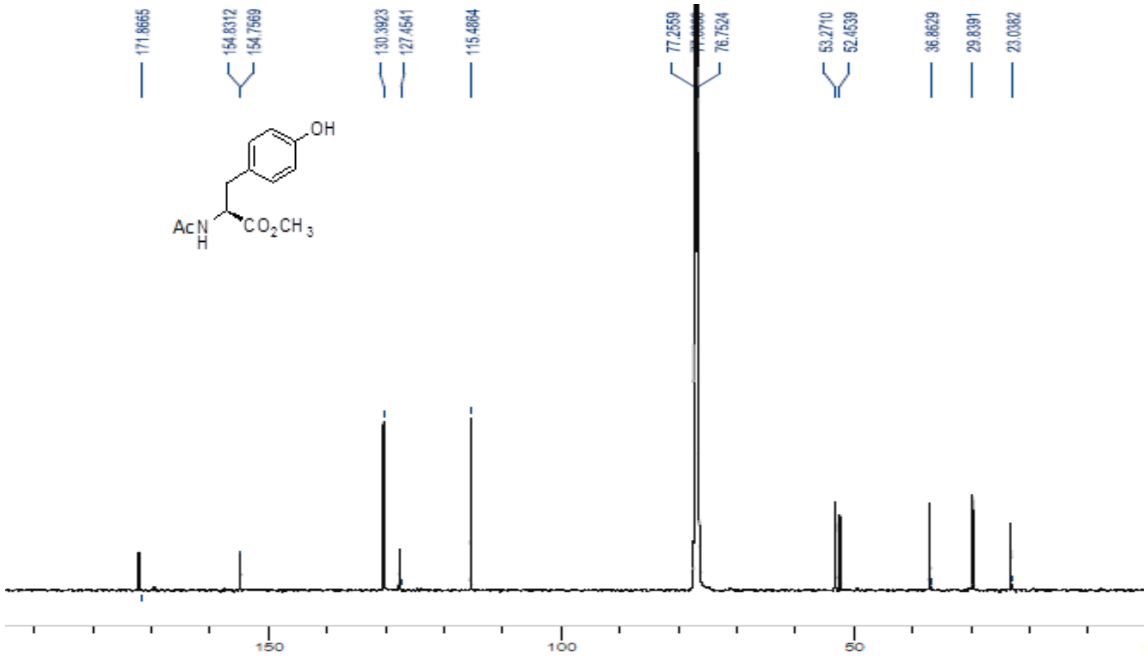
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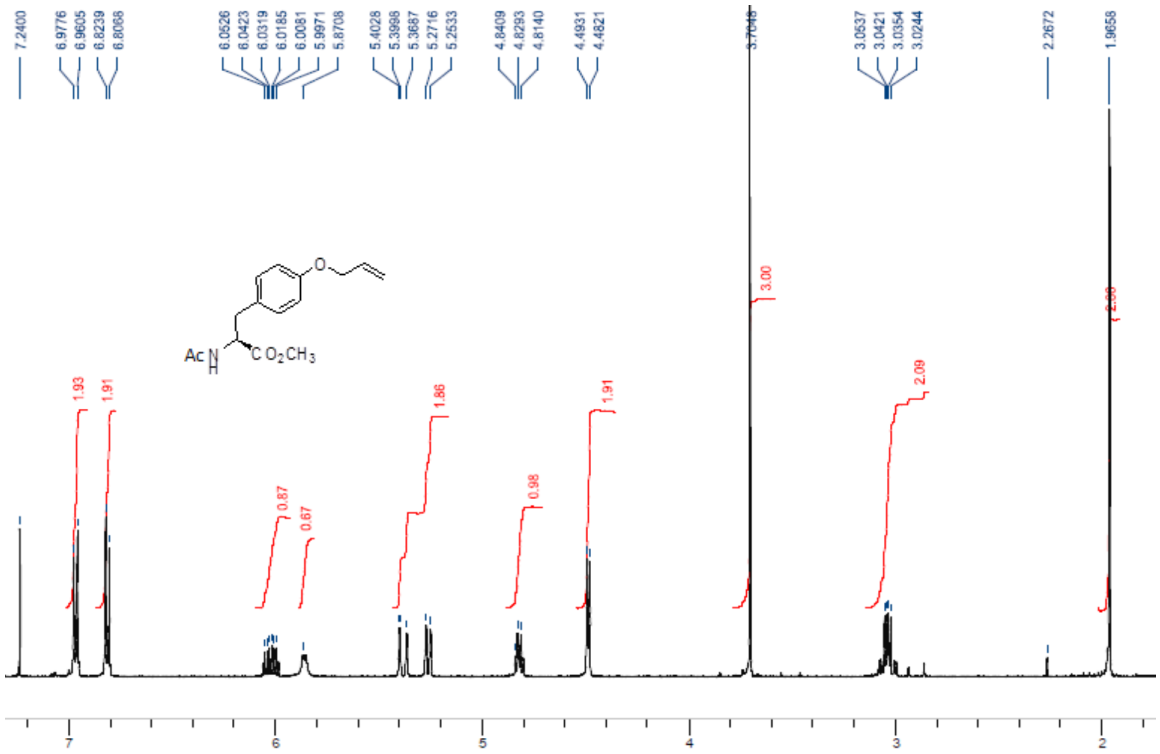
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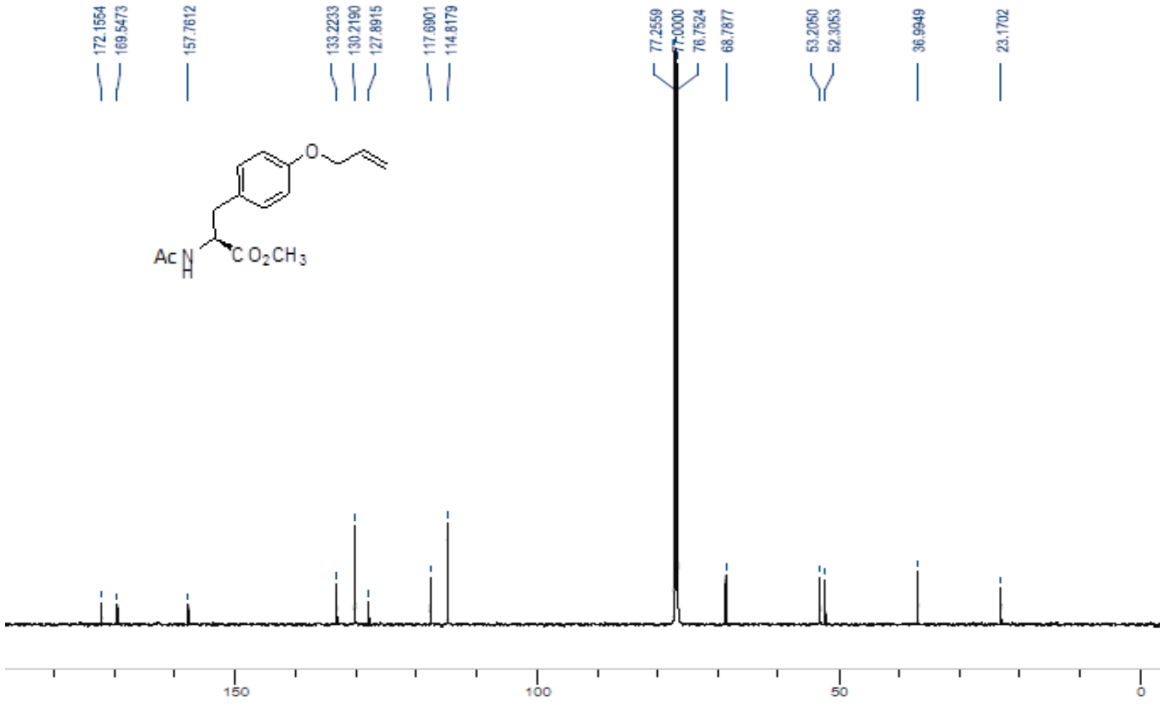
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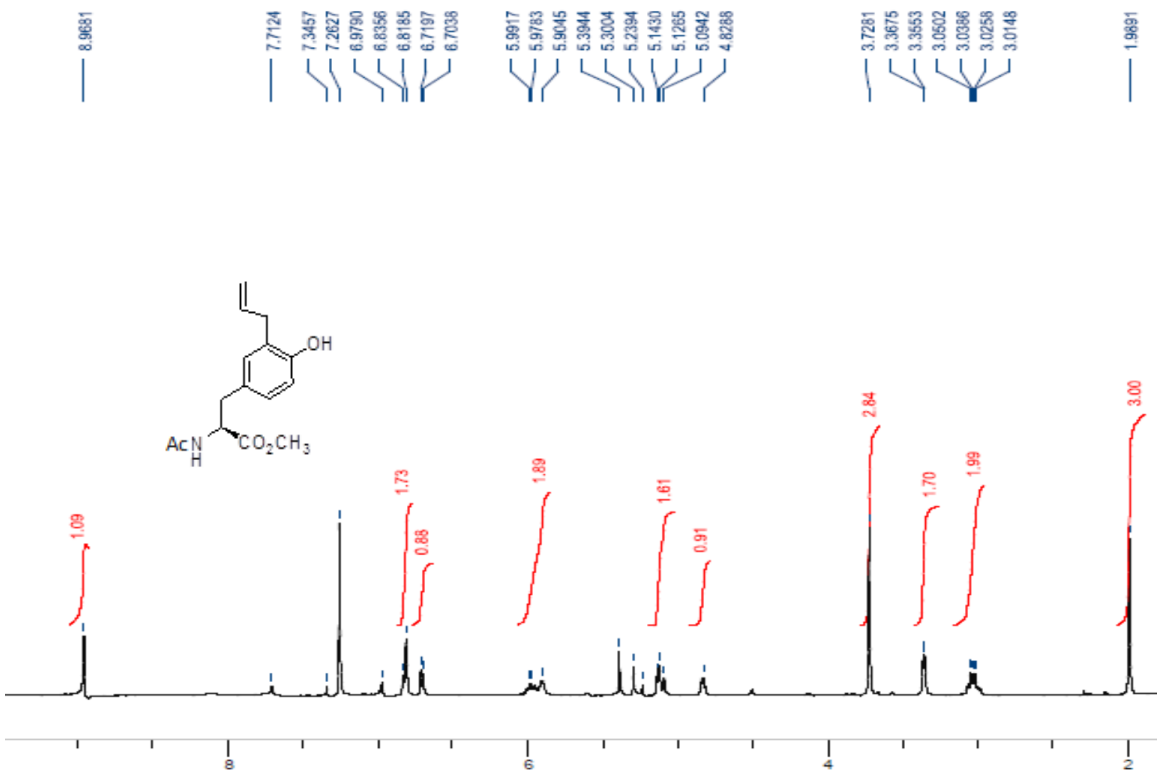
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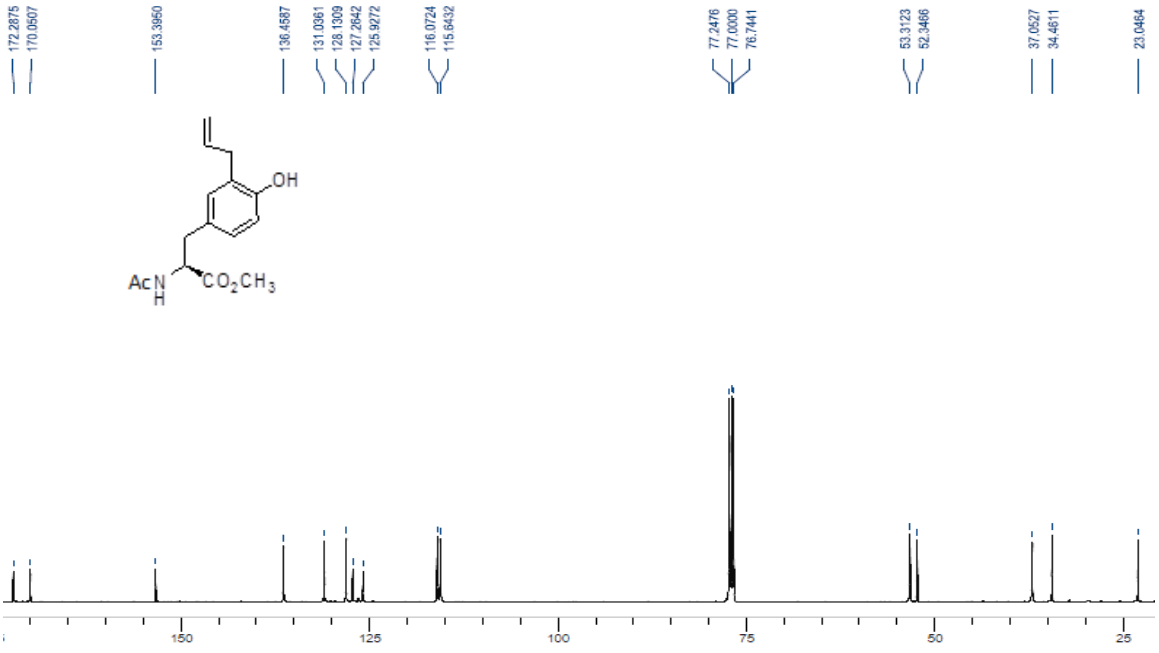
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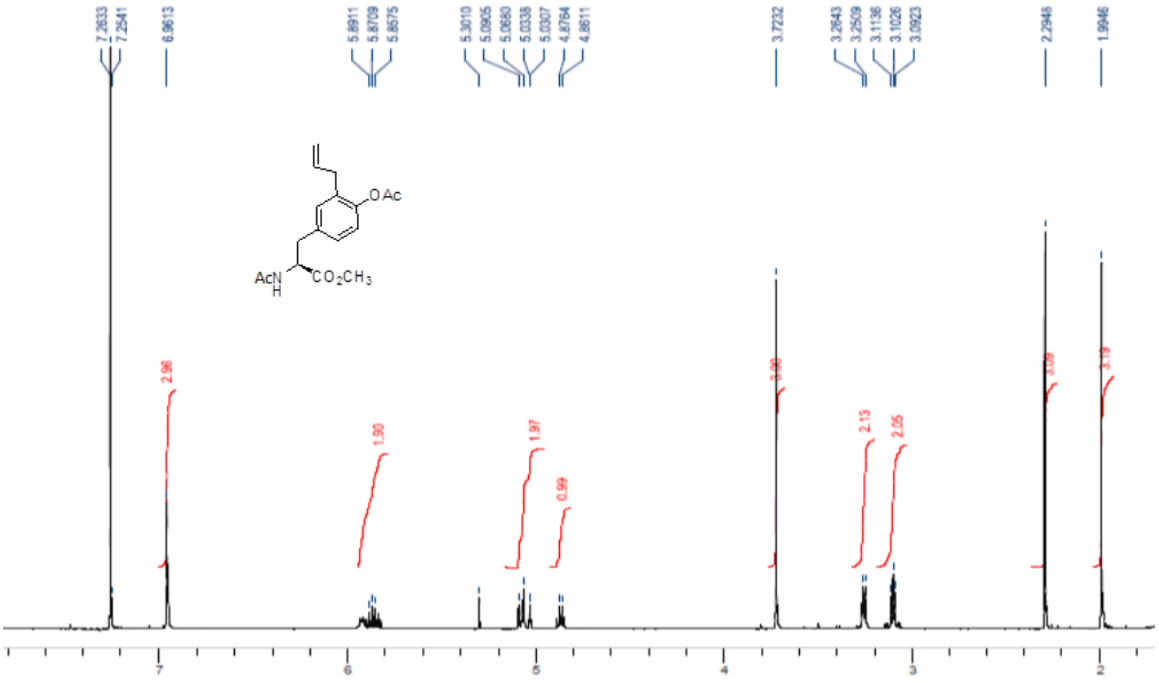
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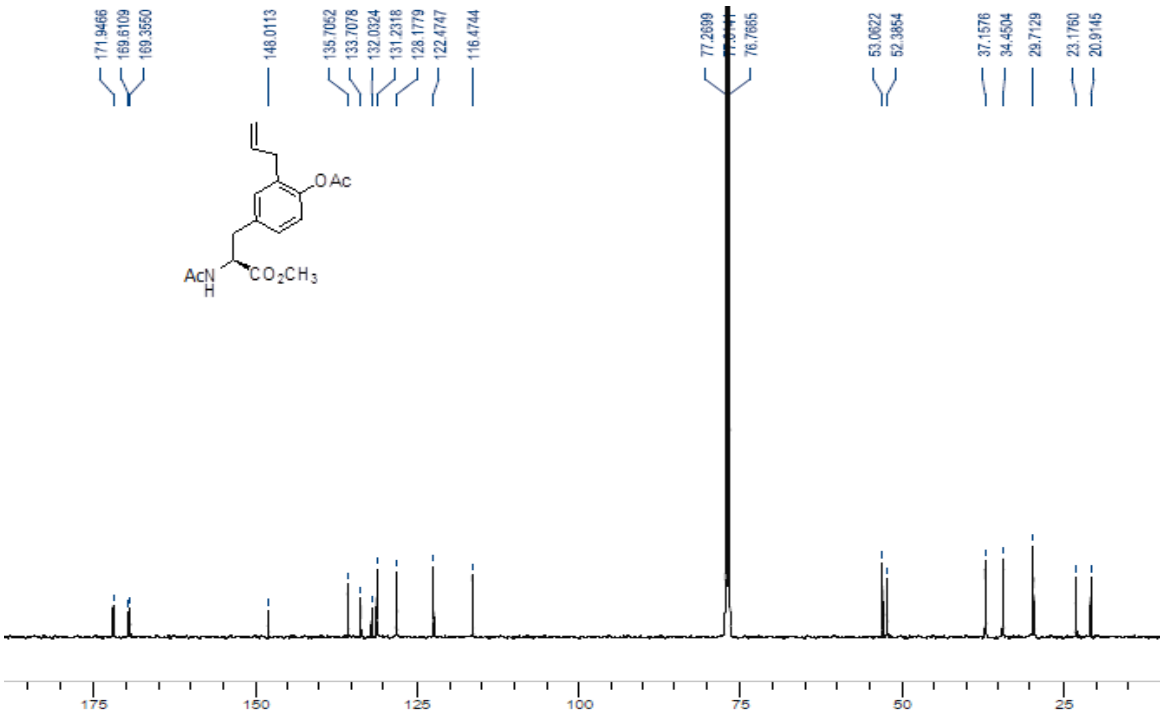
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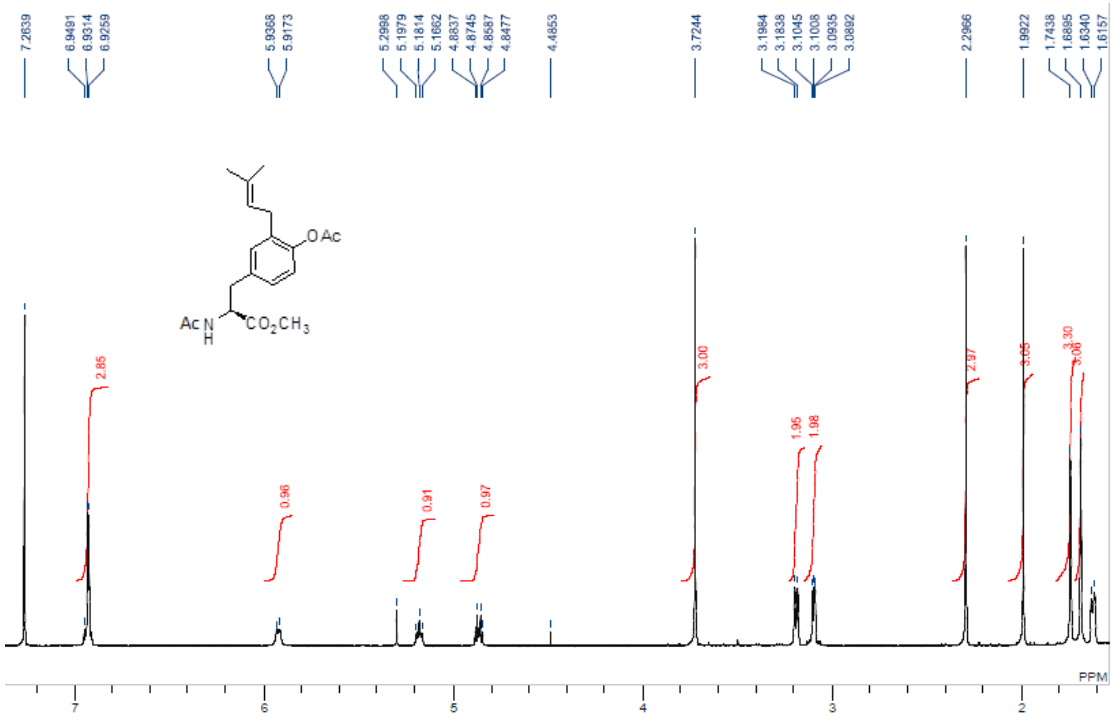
25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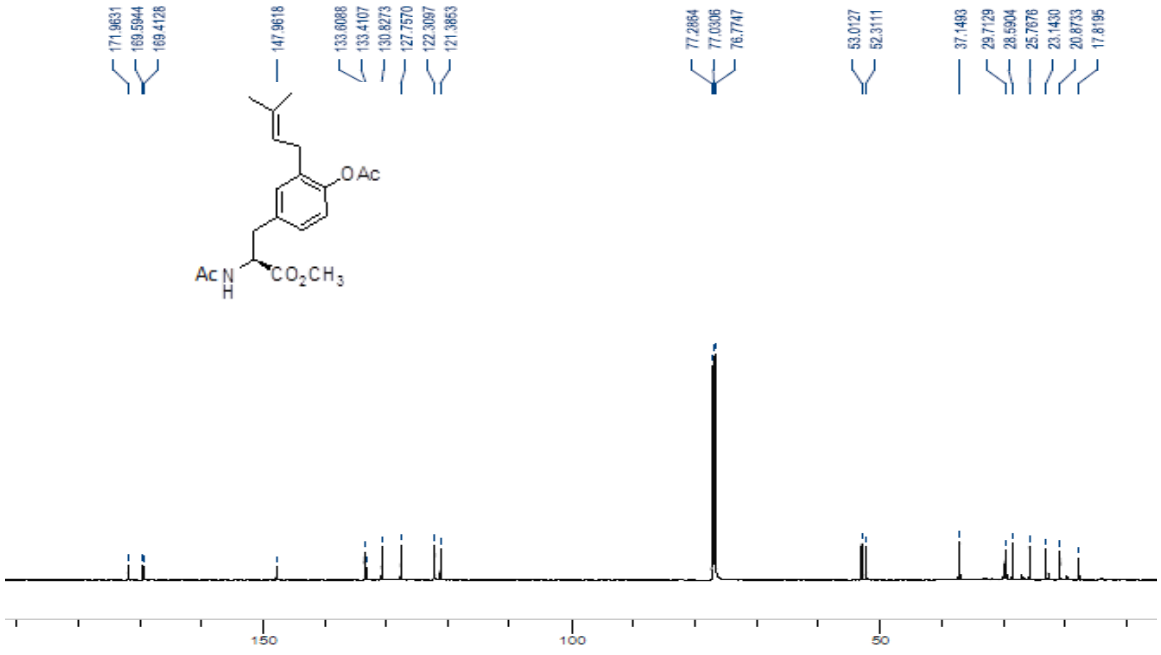
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23.1430
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OAc
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150
100
50

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Publications

1. Abbas, Y., Mansha, M. & Ullah, N. The first total synthesis of potent antitumoral (±)-mafaicheenamine A, unnatural 6-fluoromafaicheenamine A and expedient synthesis of clausine E. ***RSC Adv.*** *6*, 26104–26110 (2016).

2. Mansha, M., Abbas, Y. & Ullah, N. Microwave-Assisted Claisen Rearrangement: Synthesis of Naturally Occurring TRAIL-Resistance-Overcoming Tyrosine Derivative. ***Synth. Commun.*** *45*, 599–604 (2015).